I N D E X

BREAKOUT GROUP DISCUSSION - AVIAN

February 24, 2000

KEYNOTE: "---" Indicates inaudible in transcript.

BREAKOUT GROUP DISCUSSION - AVIAN

(8:37 a.m.)

CHAIRMAN WAGES: Good morning. It doesn't take a mental giant to figure out the numbers have dwindled. What we would like to do first off is I want to go back, Jeff. I want to just go back and read, real quick, what we have done and then dispel that. And then, when we review at the end, we will just go from where we started this morning.

When we looked at our first question, we went to define the model and critique it. Knowing the Framework Document and categorizing the drugs were important. Then we tried to design that model and said what a pre-approval study should do. You can read it as well as I can.

We defined our bacteria that we were interested in in these pre-approval studies. If you will, define the impact of the drug on pathogen load. Now, I have got a problem with that because we got down to the bottom and said that was irrelevant. So I would strike that and not mention pathogen load until we say that it is not relevant later on. Correct? So I would take three out. That is why I wanted to do this again.

We want to define the objective of the study and outcomes and results; define approvable parameters. I am not sure what that means, but I will say that.

MS. KRUSHINSKIE: Is that our objectives in the

front?

DR. GILBERT: I think that goes back to what Dennis was saying about what are we going to do with the numbers when we get them. You know, after we get the result, what are we going to do?

MS. KRUSHINSKIE: Well, that is a good question. But my question is should that be in our objectives?

CHAIRMAN WAGES: Don't look at me for that answer. Look at your colleagues in the audience.

MS. KRUSHINSKIE: Defining the objectives and objective of the study.

DR. GILBERT: I guess it should be more like defining what we are going to do with the results.

CHAIRMAN WAGES: Define the evaluation of results? Or interpretation of evaluation of results? I think that would be good. You all did very good. You must have got a good night's sleep.

(Pause.)

CHAIRMAN WAGES: Okay. Now, we are going to address the compound and define its class, its spectrum and its potential to impact resistance and, I think, the mechanism. Yes. The mechanism of resistance in the field. A new hurdle for FDA; what kind of and how much data.

DR. GILBERT: These are just comments that were made.

CHAIRMAN WAGES: Now, do you all want me to clean this up? Or do you want me to put these --

MS. : Yes. That is mumbo-jumbo. We have to clean that up. Yes.

DR. GILBERT: All right. Do you want to take all of that out? Or --

CHAIRMAN WAGES: Yes. I mean, things that doesn't really impact what I need to say. If somebody has an important comment, we want to make sure that it gets on here to represent -- although we did have a minority of one vote, and I think I threw it out yesterday. Yes, sir?

DR. WEBER: It may come up later, but one of -- these issues about the results of other issues to be concerned with. The subject was broached yesterday, but the potential importance of background or baseline data in the species, the resistance background, and potentially even humans for possible, you know, decisions later on about -- you know, if we don't have that kind of information, where will the agency get it? Is that something we are going to discuss later?

CHAIRMAN WAGES: Well, one of the questions is alternative approaches or if you had to answer this question, if you had to set up or design. And let's put out whether it be pre-approval, whatever; if this group had to define or design a way to answer the question on how a compound used in

food animals impacts food-borne illness in humans.

That might play a part in it where we could say baseline data, if I am hearing you right. That is what we need; to know what changes are occurring after the drug approval. So I think we can maybe broach that when we are going to get to the question, all right, if you had your druthers, how would you address this question, throwing out that it has to be a pre-approval.

So, if we don't do that, I sure would like to come back because I think that was mentioned a few times about baseline data so you have got something to compare with.

DR. MEVIUS: I think there is something mentioned about baseline data. Mechanism, what is in the field. That is also sort of baseline data. Isn't that meant there?

CHAIRMAN WAGES: Do you want to add? Go ahead and put it and take all the questions out? Mechanisms, what is in the field and baseline information?

DR. MEVIUS: Yes. Something like that.

CHAIRMAN WAGES: Baseline information on resistance. Okay.

(Pause.)

CHAIRMAN WAGES: I think it was brought up many times, the importance of dosage. I don't think we ever came to an agreement whether that dosage now has historically been based on -- and I am just interpreting what I heard

yesterday. Dosage has been based on efficacy and the target organism historically.

Now we are looking at that, and are we coupling that with the dosage that would minimize resistance? Is that what I heard yesterday? Or is that --

DR. MEVIUS: The point I was trying to make several times is that one of the positive aspects of these kind of exercises could be those of maturation also with respect to resistance selection. So that could be taken into account either at pre-approval studies or development of the drug. So I don't know really how to phrase that in a short sentence, but --

CHAIRMAN WAGES: Well, I heard optimize dosage yesterday a lot. Would that be an appropriate term to put in here?

DR. GILBERT: We have got that, I think, down below. Remember, with the asterisk? Remember, that ties in the doses and it says something about optimize the dose for resistance and for effectiveness?

CHAIRMAN WAGES: Okay. I will take your word for it.

DR. GILBERT: I think this comment had to do with the study should focus on, you know, only study the drug as applied for let's say seven days at this day, rather than let's don't feed the jar. You know, inject containers for a

month or something.

CHAIRMAN WAGES: Okay. Management. What will with the data post-approval? I don't know if that is the way we want to leave that, but it was a very -- it was brought out yesterday. At least what I heard was that we are going to collect this and what are we going to do with it and exactly how is it going to be used.

Dennis, you brought some of that up I believe. Does that capture -- I mean, if I say that statement, that is not going to make a lot of sense. Is there any way that you want to refine that to make it sound a little better?

DR. GILBERT: I think about --- management. Was that the correct spelling?

CHAIRMAN WAGES: How about that?

MR. : I think what we really want to know, and correct me if I am wrong, is will the information be considered pivotal or non-pivotal. Is it non-pivotal where we are gathering information so that we can make educated decisions in the future of the product or are we considering it pivotal that we need to make some sort of decision prior to approval?

CHAIRMAN WAGES: Does pivotal mean required?

DR. KOTARSKI: I think that you should specify required versus decision-making for drug registration. Every time you use the word pivotal, don't use the word pivotal.

Say required information versus required information to make a decision of registration.

CHAIRMAN WAGES: Okay. And this is -- you know, I am just trying to understand. What is the difference? I mean, what is the difference of it? Why would it be required if it would not be required to make a decision. Maybe I don't know enough about the approval.

DR. KOTARSKI: It is required to know the drug class.

CHAIRMAN WAGES: Correct.

DR. KOTARSKI: It is not a pass/fail situation because it is a macrolide or it is a tetracycline, but it is required to know what class of drug it is and what characteristic it is.

CHAIRMAN WAGES: Okay. But if you want to split hairs, if you didn't have the class on there, your NADA would be incomplete and you wouldn't be able to go forward anyway. So it is required, you know.

MR. : But it has to be pass/fail. I think that is the key in this. That is what we need to separate; is this information that we need to have that will be required, but it doesn't affect whether it is a pass/fail decision or not.

CHAIRMAN WAGES: Okay. I played a few years without my helmet. So, you know.

DR. MEVIUS: On the positive aspects of this required information, it wouldn't be -- even if it wouldn't to a pass/fail, you would at least have an understanding of potential better control of the problem.

CHAIRMAN WAGES: Take pivotal and non-pivotal out. I like the required versus --

DR. MEVIUS: Pass/fail.

CHAIRMAN WAGES: Yes. Pass/fail required or something like that.

DR. LATHERS: I guess you could ask the question of whether the data from pre-approval studies would be used at some point post-approval to estimate whether a given -- and I don't know if this is where the word threshold should be used or not; has been reached or an alarm bell has been rung.

You know, if you have some indication from your pre-approval study as to what you are looking for and the time. I guess the rate of change.

CHAIRMAN WAGES: So you want to qualify that a little bit. Would the pre-approval data be either useful interpretation of post-approval results or post-approval information. Correct? Is that what you are saying?

DR. LATHERS: Yes.

CHAIRMAN WAGES: Okay.

DR. GILBERT: Let me ask Nick Weber a question about this; is it going to be used in the decision-making

process. Nick, do you see this as a piece of the human food safety data package on the 356V? Is this going to be -- will this bear on that?

DR. WEBER: I would feel that the information is needed pre-approval, but for the reasons Claire just pointed out. I think to make those decisions; to see how those things move post-approval what mitigations or actions might be needed to work with producers and/or sponsors to keep that down. I think that is what Dennis is saying. We need to get a database knowledge about where we are starting to help influence those decisions later on.

And if you really can't do it, again the baseline data, except pre-approval before it is out there.

CHAIRMAN WAGES: Yes?

MS. : Some of this pre-approval data though, if we acknowledge that it is not -- we are working with models that are not validated as predictive models and different aspect of resistance emergence or rate of resistance emergence. Personally, I feel if you don't have a validated predictive model, you can use it as baseline information.

But I question asking -- you know, given that it is not validated, predictive data, I would not recommend that it be used for -- it would be used for post-approval monitoring. In other words, to make threshold comparisons or anything

like that, because you don't know if it is predicted or not.

CHAIRMAN WAGES: And I appreciate that. But didn't we -- when we defined our model as we did, didn't we put a part of that component was to try to validate and replicate those studies? So we got that. And if we couldn't validate or replicate, then I believe that would minimize the impact of pre-approval information on post-approval. It wouldn't eliminate it, but I think that would.

If you couldn't replicate or validate the model that we put, I would think that would -- I don't believe it would eliminate its use, but it would minimize its impact.

MS. : I don't understand how resistance emergence, when it becomes -- when the resistance becomes a broad spread problem, when it is not just a local temporal problem or a local problem, it becomes a wide problem. Sometimes that takes years. Sometimes it doesn't take years. So I don't understand how you can develop a predictive model within the scope of a registration plan.

I understand how you can replicate a different type of -- a model system and field trials, but I don't know how you can know whether or not it would be predictive short-term or long-term, because sometimes resistance emerges widespread.

CHAIRMAN WAGES: But just asking that -- and then I will get you in the back -- will the data pre-approval yield

a baseline for post-approval monitoring? Isn't that a fair question or assessment the way that stands at least? I mean, we don't know the answer to that. We would hope it would, but it may not. Okay? Yes, sir.

MR. LUTHER: I just think it has to be validated before you can use it for pre-approval or post-approval.

CHAIRMAN WAGES: That is what I thought.

MR. LUTHER: Unless validated, it is not value.

CHAIRMAN WAGES: I thought that, but I didn't know. Dennis?

MR. COPELAND: But I think there are certain kinds of information you could collect, like susceptibility data, PK data; those sort of things. Right now, whether that goes on the label or not is optional, but I think everybody agrees it is good information to have. It certainly plays into the prudent use issue because you are providing the user with the information they need to make the best therapeutic decision.

And those kinds of studies can be done in a validated way. Certainly susceptibility data can be generated under NCCLS and GLPs and the PK studies can be done in the GLPs.

CHAIRMAN WAGES: Okay.

MR. : I was just going to say if you are looking at a model that is going to give you -- it is going to quantify something for some event down the road, you are

right. Then the validation is important. But when I listened to the conversation over these last days, part of what we are trying to do is just gather information and make qualitative decisions.

So, for example, you may not know how fast the resistance mechanism was transferred, but just knowing what that resistance mechanism is is important information, whether or not it is a quantifiable thing. At least it is a piece of information we can include on the list. It is certainly going to help demonstrate in any post-approval studies. So qualitative information is important as well.

CHAIRMAN WAGES: Okay. Ties to the most doses and define -- whoa. Yes. I am sorry.

DR. LATHERS: I would still go back and ask a question. Will data, pre-approval, yield the baseline for post-approval monitoring? What happens if it doesn't when you are finally into that post-approval monitoring period? Do you then ask the question modify the protocol? Or do you make another scientific decision about that product in poultry and its future?

So, if it does provide a baseline for monitoring, fine. But what happens if, when we get there, there is no correlation? Then what?

DR. COPELAND: I think it depends on what we mean by baseline. My feeling was that we are talking about

baseline susceptibility data. It can be more than that. But certainly, for susceptibility data, it is what it is. Collecting that data prior to approval, that is certain to your baseline because that is -- theoretically, that is what it was before the problem was introduced.

CHAIRMAN WAGES: I guess I would interpret that it has to do something. You collect a baseline and that data has to go somewhere. It is either going to stay the same, go up or go down. I can't believe, if you collect post-approval data, that you can get some inference for, you know, its impact on resistance if you will. At least in a certain time period.

MS. : What if the data suggests that perhaps our original protocol design isn't the best, that there might be a better design, a study design? Do we make some changes at that point? Or do we continue for comparison purposes?

CHAIRMAN WAGES: You need to ask your colleagues that.

MS. : I am.

DR. CALVERT: Let me throw something in here that may stir things up. Realistically speaking, if you have a public health problem, sometimes you have to make a decision rapidly without appropriate data. So, in one sense, we are talking about something where the data that is there pre-approval you want to be the most solid, most complete,

most thorough information, because if something happens down the line, you may not have time to modify a protocol. You may not have time to go out in the field and test something and see what is going to happen.

You may have to simply say, okay, this is what I have got, this is what is happening, I have to decide. And being placed in that decision -- I come from the post-market side of drugs. Okay? But having been placed in that position with human drugs, I would think here you want to make your pre-approval data as complete and thorough as you can make it.

So I just put that in, in terms of your asking questions. Does it really apply afterwards? In a lot of cases it may not matter. You have to make an assessment at the point where you have to make a public health decision.

CO-CHAIRMAN GRAU: Bill, could you just state your name and what you do.

DR. CALVERT: I'm Bill Calvert, and I'm the new division director in the epidemiology division in the Office of Surveillance and Compliance at CVM.

CO-CHAIRMAN GRAU: Thank you.

CHAIRMAN WAGES: Any comments on that comment?

(No response.)

CHAIRMAN WAGES: I will just officially. From a perspective -- making big decisions with no data bothers me.

DR. CALVERT: Of course.

CHAIRMAN WAGES: And we have too much of that done already.

DR. CALVERT: But that is why I make this point; is that if you wonder why we are asking for so much data sometimes, this is -- we don't like to make decisions without data either.

CHAIRMAN WAGES: Okay. Yes, Dan.

MR. : I just have a question. You are saying that there is a human concern. Well, wouldn't there be data to support this concern? Wouldn't there be data saying there is an increase in resistance? And that will give you information.

DR. CALVERT: Right. There would have to be some sort of data, but it may not be complete enough for what we, as scientists, would like to do to make the decision.

MR. : But at least there is going to be some data out there. I mean, the concern is going to be raised by a piece of data.

DR. CALVERT: Right.

MR. : So monitor the program that says there might be a problem here; we have to make decisions.

DR. CALVERT: But the pre-market data is something that you always go back to check.

CHAIRMAN WAGES: Okay. We need to keep moving.

Should we at least -- do we capture that this data is important? I mean, do we capture the importance of the data and how -- the potential it has for use either by interpretation of the CVM management or the companies? I mean, we are going to beat this horse to death and get nothing else done.

Does it capture what I need to put out? There is always the docket and further comments can be addressed. If this captures the general drift of what we are trying to say, -- yes?

DR. WEBER: One of the issues there -- and I see the term a little bit later, the NARMS information. And I think Dennis and I are thinking along the same lines, the susceptibility issues pre-approval are --- for baseline, but wouldn't it -- to my mind that means a kind of NARMS type information pre-approval so that when you go post-approval and it becomes officially part of NARMS, if we can, you know, we should make a mechanism to fit that in so you can detect changes perhaps on that side better, linked to or not linked to human concerns on the post-approval side as well.

CHAIRMAN WAGES: You mean under NARMS we should have NARMS involvement pre and post-approval? How is that? Would that capture it? Down here. Yes. Post and pre-approval monitoring. Put via NARMS.

DR. KOTARSKI: Because really, the comparisons that

you are speaking of, what do you need to compare? You need to compare against baseline surveillance data pre-approval of that drug. Correct?

And if we had a robust NARMS that had good geographic distribution with time that wasn't, you know, biased by temporal resolutions or geographic distributions, if we had that, and we had a collection of isolates that we could tap into as companies to go and say, okay, over the past three years this was the MIC distribution for these isolates and establish a good baseline, then that would help you understand better if there was a change. But right now that program is such that it is in its developing phases, and it is not sufficiently robust to help us do that.

CHAIRMAN WAGES: Okay. Very good.

DR. WEBER: I think we have to be sensitive to if there any kind of problems there and the proprietary nature of the compound pre-approval; to somehow work out so we can get equivalent type data and the same methodologies selection for figures or whatever, but get that kind of data with that kind of sensitivity. So that is something that we can -- want to say, oh, but we can't do that. Let's try to figure out how to do that.

CHAIRMAN WAGES: Okay. All right. Let's go on down. Medication strategies, guidelines, control or resistance, focus on dose, regimens sought, and I think we

had dose already. But maybe we just -- yes.

Not practical to investigate every bug/drug. Sorry. I'm at a brain low. What do we mean by that? Not practical? I mean, I know what it means, but is that really pertinent to what we need?

DR. GILBERT: There was discussion on do we need to look at every bug/drug of the chicken and its antibiotic rate? Or do we just need to focus on the two and three that we talked about?

CHAIRMAN WAGES: But haven't we --

DR. GILBERT: We kind of did that.

CHAIRMAN WAGES: Yes. We have got our salmonellas in a row, commensals and our organisms identification. Okay. Why look at other doses? Okay. We have talked about our doses and optimizing dose. Seriously, if we take something out that you all have a problem with, please, don't let me get on a roll here cutting and pasting. While he is cutting and pasting.

Induction of transfer or the issues. I think we all agree with that, as far as resistance. And the drug categorization. Now, we did make some comments yesterday, and I want to put it in my mind. What did we say about the pre-approval information involved in categorizing? We basically said that when you guys come with your package, you have got a pretty good idea what category that would be

placed in. So we are really not impacting in the decision process of categorizing based on our information on pre-approval. Is that correct?

DR. KOTARSKI: One, two, three? Can I ask a question? Categorization one, two, three we might not. We would want to know up front. But high, medium and low exposure, that is part of the pre-approval process. I am asking that question. Is that correct?

DR. LATHERS: Ask your colleagues.

DR. KOTARSKI: Because, for example, if you had a drug that is very unstable, you found that wonder drug that was -- you know, you inject it; it is active in the animal. As soon as it starts being excreted, it falls apart. So even though it is a category one, it is exposure by that nature, the fact that you introduce perennially. That would mitigate its exposure level. Then that would be possible via data.

CHAIRMAN WAGES: I would agree with that.

DR. WEBER: I don't think a priority -- it sounds like it would. But a priority? You would have to see whether or not -- even its temporal nature. Even if it is five hours or 50 hours, you have to see what it does. It might be gone by the time. You may not be able to detect in the feces, but if everything coming out of the animal is resistant, that would be problem.

DR. KOTARSKI: But ultimately, it relies on data to

make that evaluation.

DR. WEBER: Yes. No question. But I think those are the kind of discussions early on; as you get to some of your research information early on to it. Start interacting right from the beginning with the agency on the categorizations and move toward protocols and those kind of studies that will ultimately need to be either expanded or, you know, that is as far as we go there as we learn more.

CHAIRMAN WAGES: Okay. Yes, sir.

DR. MEVIUS: A question about induction and transfer issues. Bacteriologically, induction is induction of genes that already present. So what is exactly meant there? I think we mean something else.

DR. KRUSHINSKIE: I heard you talking about the commensals. Didn't you make that comment?

DR. MEVIUS: Well, now I'm reading it. I don't know what.

(Laughter.)

DR. MEVIUS: I think we would want to know whether it is transferable resistance, whether we know the genius or not.

DR. KRUSHINSKIE: That has been addressed already.

CHAIRMAN WAGES: Then we need to take that out, because the mechanisms of resistance were already covered.

DR. KRUSHINSKIE: I think that had come right after

we were talking about all the commensals in the gut.

CHAIRMAN WAGES: Okay. Question -- yes?

DR. LATHERS: I think Jeff needs to go back and just add something in terms of drug categorization to reflect some of the discussion that was just said in terms of high, medium and low sensitivities, pre-approval study designs.

DR. GILBERT: Over what? A firm should have an idea of the categorization before --

DR. LATHERS: Data to support. Data to support one, two or three. Excuse me. Data to support high, medium and low sensitivity. Sorry.

CHAIRMAN WAGES: Okay. Now you have got me.

DR. LATHERS: High, medium and low exposure.

DR. CARNIVALE: A comment?

CHAIRMAN WAGES: Yes.

DR. CARNIVALE: Let me just point out that in the AHI comments -- excuse me. I still have a cold. The AHI comments back on the framework document, I think back in May or June -- whenever we submitted those -- we had reasoned that the exposure part of the categorization was likely irrelevant in the whole scheme of whether a drug was important to human medicine or not.

So I don't think AHI would really be big on worrying about these high, medium or low aspects of categorization, because if a drug is important to human

medicine, it is going to be a category one, regardless of whether it is used in feed or whether it is injected or whether it is only given to individual animals.

In our view, that was an unnecessary component of the qualitative risk assessment or hazard identification in the framework.

DR. KOTARSKI: And what does this group think?

DR. MEVIUS: I think if you have a drug, a compound, an active substance as category one, two or three, and the data that you will provide will show whether the way it is dosed it will be -- also will be a risk. There will be a transfer risk if the drug is a category one compound. But it is degraded in the drug very rapidly. It will not select resistance.

Well, then you have support of data that, in your specific dosage formulation, there is no risk. So just to support although it is category one in the specific -- that comes to my point on dose optimization.

DR. GILBERT: I think that is a good point, because it lends some flexibility for us. If it is just one, two, three, there is no decision making there.

DR. WEBER: But isn't it true? I think I understand AHI's statement. Basically it is -- you know, if there a category one, something really -- a silver bullet to the human arsenal, CDC and a lot of other people besides us

are going to be looking at that human outcome and any impact on that concern.

DR. CARNIVALE: Well, that is right.

DR. WEBER: If it is low exposure, then hopefully you won't see any change here in the human side, which means good. You know, that it is useful here in the agricultural side.

CHAIRMAN WAGES: Yes.

DR. COPELAND: I think you are painting a scenario where the drug degrades rapidly and would have no impact on commensal organisms. And in that case, it may not have any human health impact, even though it is a very important drug for human health. So I think that is a good point.

I think there does need to be some flexibility in the categorization to take those sort of things into consideration.

CHAIRMAN WAGES: All right. Does that statement capture what I need to say? Bottom line. Drug categorization by CVM is important; however, sponsors should have data to support high, medium -- or the exposure level. Just put -- does that capture what we want to say this afternoon? Very easy. Just nod yes or no.

MR. RUPP: Are we saying drug categorization by CVM must be flexible based on the scientific data?

CHAIRMAN WAGES: I have no problem.

MR. : That is a good idea.

CHAIRMAN WAGES: That sounds a lot -- palatable.

DR. MEVIUS: Otherwise it would be -- it would be a political decision; that category one antibiotics are not allowed to be used. That is also clear. But then you won't have to provide any data. Otherwise you should have a flexible system.

DR. GILBERT: Do you want shall, should or must?

(Chorus of "must".)

DR. KOTARSKI: What about the -- a sponsor should have data to support high, medium and low exposure. If we know that the exposure is going to be high, why should we have to have data to support that it is going to be high? The question is if we want to support that it is low exposure, then we have to have data to support lower exposure.

DR. KRUSHINSKIE: You should say sponsors should have the ability to provide data to support medium --

CHAIRMAN WAGES: Level of exposure, period.

MR. RUPP: Irregardless of what level it is.

CHAIRMAN WAGES: Yes. Okay.

(Pause.)

CHAIRMAN WAGES: Must have the ability. Okay. Let's go.

DR. CARNIVALE: Just one other quick comment.

CHAIRMAN WAGES: No. I am sorry.

MR. : Come on, man. Stop it.

CHAIRMAN WAGES: I have got an early flight at noon. I am going to give my presentation early. No. I am kidding. Go ahead.

DR. CARNIVALE: No. I just wanted to point out that high, medium and low exposure in the framework document was related to how many animals were potentially treated with the drug. It didn't have anything to do with what the pharmacokinetics might be.

DR. GILBERT: That is right.

DR. CARNIVALE: So that is why our comments were saying it didn't matter about how many animals were treated. This is bringing up a different issue. So that is fine. I just wanted to clarify that.

CHAIRMAN WAGES: So is this going to muddy the water then, Richard? Rich, is that going to --

DR. WEBER: --- put that all together in their risk assessment.

CHAIRMAN WAGES: Speak loud now. Nick, you have got to speak up. You can't whisper.

DR. WEBER: I don't believe we have put this all together. I mean, this can be a recommendation. But, you know, as I mentioned before, I think, if there is an important drug out there for human use, the agency is not

going to look at it at post-approval just, you know, because initially there isn't shown any significant -- or say you are running your studies and you see no resistance development and it is a medium category, whatever the use is.

There is no way that CDC is not going to monitor that, just like there is no way that they are not going to look at resistance. They are going to do it, and we have to be aware of that. That is going to be input data, as far as background information of where we started. You know, somebody is going to ask where that started.

And don't get me wrong. I have not been any significant role in looking at the policy issues developing around that framework document, where that is going. I am on another team and am just getting involved in that. I think we still have to hear what Dr. Sundlof and others are -- but giving him input like this ---

DR. GILBERT: In light of what Rick said, do we need to take that off and just leave it CVM must be flexible? Because truly, it has to do with how many animals you are going to be treating. The bacterial.

DR. COPELAND: Or ability to provide data to support the categorization rather than exposure.

DR. GILBERT: Or the categories.

DR. COPELAND: Or the categories.

DR. KOTARSKI: In context of the tenor of exposure

to the drug -- and that was the issue. But if you have a drug that is degradable, I mean that effects exposure, ultimately, to the bacteria, which is -- you know, impact resistance emerges. And so, if you have strong data to show that you have a category one drug due to cross-resistance to a very important drug in human medicine, but this drug has different characteristics, such that it falls apart, why can't that be considered? I would like to have that flexibility to come forward.

CHAIRMAN WAGES: How do you want that to -- I mean, does that capture it?

DR. KOTARSKI: Yes. I think you can take out exposure.

DR. COPELAND: Take another scenario, and this isn't likely to happen I agree. Suppose somebody comes up with a mechanism that the bug is not able to counter. Okay? So there is no resistance problem. Then where is the human health impact? There isn't any. Right? Even though it is going to be a very important drug for humans.

So I don't think I would just restrict this to exposure. I think the sponsor should have the ability to demonstrate, for whatever reason, that this particular drug should be put in a different category then what you would normally put it in because of -- whatever the characteristics of that drug.

DR. KOTARSKI: Unique characteristics.

MR. RUPP: Because they categorize the resistance for that compound.

DR. COPELAND: Right.

CHAIRMAN WAGES: Yes. Period and throw out the next one. How about that guys? Is that okay? Yes? Yes. All in favor to have that go? Pardon me?

MS. : A change in the categorization.

MR. : To support a change in the categorization.

CHAIRMAN WAGES: To provide data to support a change in the categorization. All right. I just want to go on record. It is going to be a miracle if I can convey these points accurately this afternoon. I just want you all to know that, and I am catching a plane real quick when I am done.

(Laughter.)

DR. MEVIUS: I think that it wouldn't change the categorization. It would only change what is done with it. I think you would categorize a specific group of drugs, but the flexibility we would ask, or I would ask, is how to deal with -- if you provide data to show that there is no risk at all, then yes. So the flexibility of the data, but not the categorization. It would still be a very important drug.

If you could show, pre-approval and post-approval,

that nothing is happening, it should be allowed. Yes?

CHAIRMAN WAGES: I agree. But that --

DR. MEVIUS: There is no change in categorization. It still would be important and CDC would monitor that ---

MR. RUPP: I agree with you, but I think that is where the science has to be -- then become regulation. And if CVM is going to do this categorization in which you start off in that categorization, there has to be a mechanism for CVM or somebody to say -- because that is going to tie to what your requirements are, if you are in a categorization.

So there has to be a mechanism in which CVM and the sponsor say -- I agree with you scientifically. How you do that regulatory-wise is -- there has to be something for them to say it is no longer going to have to be required to do the category -- or the category one. It needs to do category two or three. I am thinking of the mechanism when you have to regulate.

DR. MEVIUS: The problem is -- if you listen to Frank Anguelo --

CHAIRMAN WAGES: Oh, the "F" word.

DR. MEVIUS: --- to CDC or whatever, things happen. And we are monitoring post-approval for these rare events and things are changing, things are dynamic, and so the category one will remain a category one, and we are monitoring for these things that may be dynamic and changing

in the future.

CHAIRMAN WAGES: Okay, Nick. Last one here, and we have got to make a decision and go on. Okay?

DR. WEBER: I think we have gotten pretty far afield into the public policies and the management issues, as opposed to protocol issues and things like that. And I agree. We haven't -- we really haven't had that big a discussion yet, publicly, about the framework and threshold and that sort of thing.

Again, we hear you. We will take some of these things back. If there is some miracle bug that doesn't get resistant to anything, show me, you know.

CHAIRMAN WAGES: Does that --

DR. WEBER: Let's move on to the protocol issues.

CHAIRMAN WAGES: Is that the gist? Okay. We are going to go on. Exposure to bacteria. Take that out, please. Okay.

Question three: What factors should be considered when modeling resistance? Okay. This is -- pathogen load was not relevant in the pre-approval process. I think we will take out USDA and -- mimic field conditions; practices may be difficult. I think we acknowledged the difficulties in some of these.

What is the difference between two and three, mimic field conditions and conduct a study in the field? Should we

just put mimic field conditions as best as possible?

DR. KRUSHINSKIE: We have that study in the field.

CHAIRMAN WAGES: Yes. You can't go --

DR. KRUSHINSKIE: On the farm.

CHAIRMAN WAGES: Yes. That is tough. Changes in field studies correlate with pre-approval action. Changes in field studies correlate with pre-approval action. I have no idea what that means.

DR. GILBERT: The thought was if we started seeing differences in these areas.

DR. WEBER: If we observe any changes in resistance.

DR. GILBERT: Right.

DR. WEBER: Could you correlate it to the field, and then, would that effect -- but at least in chickens --- your research facility is probably the best for most of these species work in.

CHAIRMAN WAGES: We are going to delete that comment. Rate and extent; a post-approval consideration. Rate and extent of resistance of post-approval consideration? Is this where we want to capture that baseline information will be helpful in this?

DR. WEBER: Yes.

CHAIRMAN WAGES: I would like to put it in there if I have to do this. Rate and extent of post-approval

decision, but, however, baseline information. Pre-approval baseline information will be important. I think that is a big deal.

DR. GILBERT: Pre-approval baseline instead of that?

CHAIRMAN WAGES: Yes. Please. Pre-approval baseline information.

DR. GILBERT: More important? Or --

CHAIRMAN WAGES: Important. Imperative. I don't know. Whatever the words are. I never -- I flunked English.

DR. KRUSHINSKIE: In that baseline information you are referring to antibiotic resistance levels or any kind of baseline information?

CHAIRMAN WAGES: It is the baseline, the NARMS type baseline information.

DR. KRUSHINSKIE: Why don't you explicitly say that, because how do you know the --

CHAIRMAN WAGES: NARMS type baseline?

DR. KRUSHINSKIE: --- studies are baseline ---

CHAIRMAN WAGES: I don't think of them that way, but I am sure somebody could. Or, how about if we put NARMS in parenthesis or whatever type of baseline information. Okay.

Will any studies be a part of a risk assessment? Is that -- go ahead.

DR. WEBER: Undoubtedly. But when? Pre or post-approval?

CHAIRMAN WAGES: Okay. We won't worry about. Objectives should be human health impact.

MS. : I think we should.

MR. : Oh, come on.

CHAIRMAN WAGES: Oh. Come back.

DR. LATHERS: I think you could make an argument that some of the pre-approval data will be part of a qualitative risk assessment because, in essence, --

CHAIRMAN WAGES: Sorry about that.

DR. LATHERS: -- you are asking a question.

MR. RUPP: I still come back to my comment from yesterday; that you are doing all this data based on human health impact, that it has to be part -- it has to provide some kind of data so you have a better look at the risk assessment, because if there is no human health impact, why are you doing all of this?

CHAIRMAN WAGES: Okay. We recognize then that some of this information -- I will say that -- will be part of a risk assessment. Did you want to add -- who said qualitative? We want to put qualitative in there? Okay.

(Pause.)

CHAIRMAN WAGES: Okay. Objective should be human health impact. I think we agreed with that. Surveillance

data, baseline -- okay. What? CVM needs assurance. That just was some explanation of our other objective of human health. Pardon me?

DR. KRUSHINSKIE: We are never sure that no public health problems will arise either. We can't guarantee zero impact.

DR. WEBER: That is addressed up above.

CHAIRMAN WAGES: Yes. Take that out, please.

DR. WEBER: Basically, you can't assure. I agree. No public health. We want to get geared up and focused so we can address some human health issues as they come up.

CHAIRMAN WAGES: Human health and politics. Those are the same terms. So, let's take that out. I am sure glad Fred is not here.

(Laughter.)

CHAIRMAN WAGES: Okay. The agency. Well, that is still -- I think we just need to emphasize the purposes to assess the human health impact. "CVM needs tangible justification." I think that is important, but I think we are going to -- as we get down toward the end of asking the question of pre-approval studies in general, I heard a lot of things; that post-approval may be as important, if not more important, than pre-approval.

So, do you want to leave that or shall we bump it down into another context? All right.

DR. KOTARSKI: I thought that there was an important comment that came up yesterday. It was in context of yours. I remember you made that comment very well yesterday, that CVM has to be able to testify to Congress that they had tangible evidence for making the decision to go forward with the product for registration. Did I understand you correctly?

MS. : Well, in developing the tangible evidence. I mean, that is what the whole pre-approval --

MR. LUTHER: Well, it sort of goes like this in my mind. Fred has raised a question, and how do we address it? Somehow we have to alleviate in CDC's mind that the actions we take to improve new products are not going to adversely impact public health. If that means pre-approval studies, it means pre-approval studies. If it means post-approval studies, it means post-approval studies. I don't know what it means.

DR. GILBERT: On the next line I think somebody made the comment that CDC has no requirement for pre-approval studies or not even suggesting it. So --

MR. LUTHER: CDC is not?

DR. GILBERT: Somebody said that.

DR. KRUSHINSKIE: I do have one comment --- listening yesterday. You listened to Fred --- message. Fred said repeatedly he has a very -- he is very focused; that

category one drugs are not to be approved for food animal use, period. That is his agenda.

So, whether you call for pre-approval or not, it is a mute point if you can't use them.

DR. WEBER: I thought I heard him maybe toning it down so they are not for use for feed use.

DR. KRUSHINSKIE: He wants fluoroquinolones out, and they have been used for feed use. Never.

DR. WEBER: Well, I mean they are used broadly. They are used broadly in say drinking water. In hard use as opposed to --

DR. KRUSHINSKIE: They are used broadly.

DR. WEBER: Well, I think that is one of his concerns.

DR. KRUSHINSKIE: I wouldn't take any comfort in that, that CDC is not asking for pre-approval products. That is not true. First off, category one is no use, and below that --

CHAIRMAN WAGES: I don't think we should, as our workshop, put words in what CDC is saying or not saying. You know, so in that part -- to me, that doesn't have a lot of relevance for our group to say, one way or the other, what -- putting words in CDC's mouth.

DR. LUTHER: I would how that CVM's position ultimately comes back to the scientific position. If we

deviate from that, we are in trouble. We have to stick to science whatever we do.

CHAIRMAN WAGES: CVM needs tangible justification in the approval process. Do you want to take that -- that doesn't say much to me. If I say they need tangible justification, --

DR. LUTHER: I would say scientific justification.

DR. WEBER: Or viable science-based decisions. Something along those lines.

CHAIRMAN WAGES: Justification for what? Approving a drug? Taking a drug off?

DR. KOTARSKI: If you are going to approve -- there is a possibility to approve a category one drug. Am I understanding this correctly?

DR. LUTHER: We have done it. But whether we can keep them on the market is one of these questions.

DR. LATHERS: So aren't you saying two things? Data for pre-approval and post-approval.

CHAIRMAN WAGES: How about CVM needs tangible evidence through the pre and post-approval drug process or something like that? Would that catch it?

DR. LATHERS: Fine. That is good.

CHAIRMAN WAGES: No?

DR. KRUSHINSKIE: I don't know about scientific in there though.

CHAIRMAN WAGES: That is fine. No. Scientific -- take out tangible and put scientific-based or however. That is fine.

Okay. All right. Opportunity to collect data, optimal dosing rates, genetics or resistance in the environment. We talked about that earlier. Or does that need to still stay there? We have -- no. All right. It is history. How are we doing?

DR. LATHERS: Do we have optimal dosing rates higher up?

CHAIRMAN WAGES: We had the optimal dosing rates. Okay. Information, regulatory, pre-approval info will aid in these activities. Now, wouldn't that be what we just said basically? So take that out, please.

Concerns for what might be missed during pre-approval process. Concerns for what might be missed? Somebody help me.

MR. : That is why we do post-approval.

CHAIRMAN WAGES: We tried to capture that with --

DR. KRUSHINSKIE: Dennis, I thought part of this discussion -- we went to this discussion when we were on number three, but that is not really part of the question of three. Question number three was what factors.

CHAIRMAN WAGES: No. I think what we are going to do --

DR. KRUSHINSKIE: I mean, that should be moved somewhere else.

CHAIRMAN WAGES: Yes. I think what we are going to do is I am going to qualify that we didn't go lock-step through these. We took issues and didn't lock-step them. And sorry. It is going to jump back and forth. Qualify it for 30 seconds and go for it, if that is okay. Because I think it would take a lot of cutting and pasting and all that kind of stuff.

So I am just going to qualify it and say we didn't do it. And if they don't like it, I will pick up my toys and go home. All right. Factors. Pardon me? You have to keep a sense of humor, folks. Factors to be considered for what?

DR. KOTARSKI: Factors to considered for our objective; to address the objectives.

CHAIRMAN WAGES: I think this is three, isn't it? We will take the question parts out. That should be considering for modeling resistance.

DR. KRUSHINSKIE: See, this is all talking about an animal model. This is not baseline studies. I mean, a baseline study, a pre-approval baseline study, is a different animal than a colony house, pet trial; whatever we are talking about here. We dose them, we challenge them, et cetera. We are like mixing everything together here. I just don't think it is very organized.

DR. KOTARSKI: This conversation -- remember when we went through and we asked what are our objectives? What objectives do we have to address in terms of data gathering to address the objective of rate and extent of resistance emergence? And our studies had to take these factors into consideration for study design.

DR. KRUSHINSKIE: For a clinical study. But really, if we want to address the rate and extent, it seems to me there are several arms to that. One is baseline antibiotic resistance level monitoring in the target population, as well as the human population. I mean, that is what you want to know before you release the drug.

How much resistance is present in the human population on those camplyobacter isolates today for salmonella. How much present in the animal population in salmonella. Five years post-approval how much is present. So that is one type of study.

The second type of study is if we took 50 birds and put them in a colony house and gave them the drug, how much increase in antibiotic resistance level do we see pre-treatment versus post-treatment. Those are different studies. I think you need to list what really -- from the big picture perspective, what do we need to do first to organize our thoughts on how we are going to provide the information showing this resistance is changing?

Maybe we should make a list. You know, we want to do a field -- we want to do a baseline survey. We want to do a colony house study looking at the target pathogen, the camplyobacter, salmonella and enterococcus, et cetera. What else do we want to do? We want to collect information on what the basic underlined resistance mechanism was. What is the genetic mechanism? What is already known in the literature about this new drug that we are trying to get approved?

First we need to organize our thoughts, and then we can go to the specifics of how we would actually do each of these differently.

DR. KOTARSKI: And what you are saying is the specifics of the field study to maximize dose and minimize resistance in terms of the dosing strategy.

DR. KRUSHINSKIE: Right. And looking at how the treatment regime affects resistance in an isolated group of animals. That is a different study than looking at what is our baseline pre-existing level of resistance in salmonella today.

And that is why I think number seven should not be in this at all, because number seven is baseline information. What do we already know about this compound? What do we know? What is it related to? If it is related to another compound, what do we know about resistance mechanisms

already?

And we said clearly that if we were going to develop information on the mechanism of resistance of a brand new compound, you have got 10 years of these studies trying to figure out how its own resistance mechanism works. That is not part of a little colony house trial.

DR. KOTARSKI: I think everybody is agreeing with you.

DR. KRUSHINSKIE: Okay. So take that out of there.

CHAIRMAN WAGES: All you had to do was just say I don't think we need that.

DR. WEBER: You have got to put it somewhere. That kind of data develops --

MR. RUPP: We addressed that up front of needing to know the mechanism, needing to know that stuff and then we moved into needing baseline. I think maybe if we looked at how we define that baseline, because I was a little confused because we threw baseline around. But we talked about a lot of different baselines. Human baselines, animal baselines.

CHAIRMAN WAGES: There is mechanisms; what is in the field and baseline information on resistance and mechanisms and then the rate and extent of resistance was above that.

DR. KRUSHINSKIE: Number seven needs to go up in there. Like what is known? You know, what is the mechanism?

CHAIRMAN WAGES: So you need to qualify that more?

DR. KRUSHINSKIE: Well, I would move it into some of that, some of your supporting information.

CHAIRMAN WAGES: Can you cut that and move it up? That is fine.

DR. WEBER: You would probably get that kind of information from a very specific study. Or you would have to find specific items in the environment somewhere.

DR. KRUSHINSKIE: Or it would be pre-existing. There might be pre-existing information already.

DR. MEVIUS: Why not just list it before. This is the animal trial; requirements before that. What is baseline information, NARMS kind of information? Baseline information on mechanism, on transfer; those kind of things. That is a necessary requirement before you do -- well, also besides this kind of an animal trial.

DR. LUTHER: Where does that have to go, guys?

(Simultaneous conversation.)

DR. LUTHER: --- flip chart. Would it help for us to use a flip chart just briefly to get --

CHAIRMAN WAGES: As long as I don't have to do stand to do it and somebody else does it.

DR. LUTHER: Well, maybe David Grau would do that.

CO-CHAIRMAN GRAU: I can do that.

CHAIRMAN WAGES: I mean, I agree. This may be a

hodge-podge.

DR. KRUSHINSKIE: You don't want to get down in the trees before we have got the forest. So what kind of information do we need? We need baseline antibiotic resistance levels pre-approval and post-approval. I think we all agree that that is a critical component. Through the NARMS database or whatever.

DR. GILBERT: Do you have a time estimate on that?

DR. KRUSHINSKIE: Time? How long before and how long after?

DR. GILBERT: Like five years? How long does it take to get that information?

DR. KRUSHINSKIE: Well, what are they doing now?

DR. MEVIUS: Pre-approval recent data first of all as a baseline.

DR. KRUSHINSKIE: And then a periodic post-approval --

DR. KOTARSKI: That comes from that robust NARMS set of isolates.

DR. MEVIUS: Right. Right.

DR. KRUSHINSKIE: So that would be number one, is baseline antibiotic resistance levels, and then post-approval monitoring. Post-approval levels. Those are actually one type of studies.

MR. RUPP: But if you are talking about -- if you

are talking about post-approval, I think we need to be very specific. I don't think we can throw PAMs around lightly, because that term has been deemed something that the sponsor is going to be doing.

I think it has been very clear in this meeting that we are talking about a robust NARMS system, not what has been traditionally called a PAM, in which a company is responsible for that monitoring program. Let's be specific.

DR. COPELAND: But CVM ---

MR. RUPP: Right. I guess that is what I want to make sure is very clear. Yes.

DR. WEBER: All we are saying is this kind of data. Let's not get into who does what. This kind of information is needed so after --- we can see whether it is finished.

DR. KRUSHINSKIE: That would be item number one. Number two would be dose titration, antibiotic resistance levels during the course of dosing or however you want to call it. Clinical trials? I kind of think of those as a small scale --

DR. MEVIUS: I think before that -- first of all, also the mechanism study. Information on mechanisms could be literature or --

DR. KRUSHINSKIE: And if you have to do studies to --

DR. MEVIUS: Transferrable resistance, chromosome;

that kind of baseline --

CHAIRMAN WAGES: David just pointed -- excuse me -- that we may be getting into what role would the data play in evaluating microbial effects. I don't understand that myself. But what role could the data play in evaluating the development of resistance I guess.

CO-CHAIRMAN GRAU: Right. What would the data be and then how would you use that data in your evaluation?

CHAIRMAN WAGES: Yes. Go ahead.

DR. COPELAND: If you would allow me to use the "F" word just once, --

CHAIRMAN WAGES: It may be appropriate in this instance.

DR. COPELAND: Fred had a list of -- I think it was a list of five items that we have really not talked about specifically. I think we have covered some of them here. I know, from talking to people in other groups, that they have focused on those five times. I don't know if we want to do that, but it seems to kind of fit in here. I think mechanism of action was one of them.

CHAIRMAN WAGES: Yes.

DR. KOTARSKI: Yes. Let's just talk about the basic information. Spectrum of activity, mechanism of action, cross resistance, resistance mechanisms that are already out there that we know about. These are just

literature review types of stuff that you can --

DR. RUPP: What I was thinking, Sue, is yesterday we were pretty much -- I think we had some sort of consensus. I hate to call it a resistance characterization, but that we were going to have -- do pre-approval would be this resistance characterization.

We didn't scroll down far enough because we had detailed conversations on these models and came up where we were going to have the question today on can you really do that. I thought that consensus of the group was that we do this, this characterization of a resistance and that would allow NARMS to do a better job as far as post-approval monitoring; that we realized that we may not be able to overcome it.

I think the consensus was that we -- that model that we came down to, just scroll down -- I mean, we had this detailed conversation. I just --

DR. KOTARSKI: No. I am not disagreeing with you. What I just recounted is just something you can do in the literature review. It is just basic information --- so I am not trying to counter any of what you have suggested.

MR. RUPP: No. I agree. I just wanted to make sure that -- I mean, we had a lot of these conversations, very detailed conversations. I mean, we started going through some of this stuff, and as these comments were made,

I guess we started deleting them, and I understand why we deleted them. But then, we started to come to a conclusion yesterday afternoon based on some of those comments, and I just don't want to lose that.

CO-CHAIRMAN GRAU: Do you think it would make sense for Jeff to go to the bottom and really answer this question and say data to be collected. And do you want to divide it into data that you would collect pre-approval, data that you would collect post-approval; other kinds of data; whether they overlapped? I need your help.

And how do you want to present it? And how do you want to organize it in a way -- and then I will start filling in that information.

DR. KOTARSKI: That list I just gave you, that is a simple microbiology list. It is just an information packet of other's work.

DR. KRUSHINSKIE: Can't you just list it as that? Put, like for number two, information package about the drug on that. Like when we had baseline studies. Put that whole thing you have got there as item number. That is just one. All that is one. That is all the baseline resistance levels, pre and post-approval.

And then number two is microbiological information package, which is all -- what I got concerned about with number seven up there are the studies. I mean, you can do

studies forever. I mean, realistically, you can't -- do you want to commit to doing a whole bunch of baseline studies?

DR. KOTARSKI: Nobody is suggesting that. I think people are getting fearful about something that is very simple and straightforward. And me, as a microbiologist, I go to the literature, I have a drug, I can tell you, you know, it is easy to do spectrum of activity. Just straightforward testing.

It is easy to say do organisms that have known resistance to determine if they have cross resistance. It is easy --- literature review. That is all I am saying. So you need to provide information about spectrum of activity, resistance determinants, confer cross resistance to your drug, literature review; simple stuff.

DR. KRUSHINSKIE: Yes. Literature review. That is what I think, too. Keep it simple.

DR. KOTARSKI: Right. And then chromosomally determined versus transferred.

DR. WEBER: It is the sort of thing that she just said. Those are not difficult studies to do. You run a -- I am not going to say how to do it. I am just saying don't paint it as a picture as a 10-year study. You can get some information on the nature. Whether it is chromosomal, plasmid and something about that or fingerprint it.

DR. KRUSHINSKIE: I think my concern -- and I am

not going to be doing the study. So I am not the user end. But I would -- if I were you guys, I wouldn't want to leave that open ended.

DR. KOTARSKI: Say literature review. How is that?

DR. KRUSHINSKIE: Well, yes. That kind of stuff. But as far as doing some of those studies and all, I would just be careful not to leave it too wide open.

DR. WEBER: You don't want to put it in here that we need information on it. If the literature hasn't been done on it, -- I don't know.

DR. McDERMOTT: I would like to just ask a simple question. I think it would have been helpful at this meeting for people like myself who don't really know the drug development process very well. But you are obviously want -- don't you usually want to know the mechanism of action when you develop a new drug? And doesn't that point you pretty straight away to the mechanism of resistance? Isn't that a normal part of the development?

And it is such important information, and it is going to help immensely ---

(Simultaneous conversation.)

DR. WEBER: Wherever it comes in, we need to know -- or you know where the thing is going to have a problem even before -- you know, by the time you get to it.

DR. McDERMOTT: And I just emphasize that it is so

important because of the chaotic nature of trying to do all these pre-approval studies. You are going to be forced, in a lot of these cases -- and I don't want you to think I am speaking for CVM. I am a new guy. So I just give my opinions.

But it seems to me that most of what we are going to be able to do to protect human health in the end is to see what happens. We keep talking about the real world as in the field, but the real world is the whole world, and we are going to have to be able to watch -- keeping our eyes open is going to be the most important part of this process, and we have got to have mechanisms of resistance to have our eyes wide open.

DR. LATHERS: And if it is not in the literature, then --

CHAIRMAN WAGES: You have to get it.

DR. WEBER: You know a lot about this. He is a card carrying molecular microbiologist. He did this for a living in his previous life.

CHAIRMAN WAGES: Richard?

DR. WEBER: This is not something that, you know, takes him 10 years to find out. And your microbiologists, in developing this stuff, is going to know these things.

CHAIRMAN WAGES: Hang on. Richard?

DR. CARNIVALE: I just wanted to ask the people

from the companies. Most of these drugs come out of human discovery. So isn't this data going to be pretty well known before it even gets put into the veterinary market?

DR. KOTARSKI: I do have one concern about the -- it is the Fred list.

CHAIRMAN WAGES: You worry too much. I want you to know this.

DR. KOTARSKI: No. I don't worry about getting the spectrum of activity, but -- I won't use the word worry. Transfer resistance. Those are simple experiments to talk about resistance transfer. And, you know, he asked -- when I gave my talk yesterday, he said, can you measure rate of transfer? Yes, you can measure rate of transfer.

You know, I understand that you want to be able to identify whether or not a resistance is plasmid mediated versus chromosomal mediated. That is important information. To go and identify all the rates of transfer in all these different pure culture studies is an exercise that I don't think is very predictive, and I wouldn't want to see a lot of emphasis there if we know it is plasmid mediated, because it is not going to tell us, necessarily, the rate of transfer in the larger, broader setting.

So I wanted to have some restrictions on the amount of information that is required about rate of transfer in vitro, because I don't know what that is going to tell us.

DR. McDERMOTT: I don't think it is going to predict anything in vitro.

DR. KOTARSKI: Thank you.

DR. McDERMOTT: I don't think you can rely on it all, and everybody does it in different mediated conditions. There is so many factors involved in that alone that it is not going to have any predictive value, as far as I am concerned. But to know that it is a mechanism is going to be important.

And I wouldn't expect you have to know every mechanism, because that might take years too. Just enough information that will allow a monitoring system to at least gear up to follow that resistance --- because, you know, over years we have found -- you know, there are three or four different kind of subtle resistance, and that --- but on the front end --- deal with mechanisms it is going to be critical to at least starting any kind of monitoring --- genetic epidemiologists.

DR. GILBERT: Do you want any of that captured?

DR. KOTARSKI: Yes. I would like to have that on the record, because it is on the record that Dr. Anguelo asked the question. And I didn't say it.

CHAIRMAN WAGES: You didn't say the "F" word. Thank you.

DR. KOTARSKI: But Dr. Anguelo asked that question, and I would like, for the record, for us to address, if people agree with that concept.

CHAIRMAN WAGES: Under what Beth said about baseline studies, antibiotic resistance levels, post-approval levels and transfer studies, resistance capture studies? You want it captured it is own -- you want it in its own little bullet?

DR. KRUSHINSKIE: That is part of the packet. That is part of your microbiological information. That was my whole point, is not to make it so open ended that you --- forever.

CHAIRMAN WAGES: Put it under two.

MR. : --- try and list the specific studies that makes sense here. Can we do that?

CHAIRMAN WAGES: Do what? I am sorry.

MR. : Can we list some of these specific studies that would make sense?

DR. KRUSHINSKIE: What I would like to do is try to get the list of categories to begin with, because we have kind of gotten the --- and the clinical trials. But we don't really have a big picture laid out.

CHAIRMAN WAGES: And we are running out of time.

DR. LUTHER: Well, let Jeff do the big picture on

the computer.

DR. KRUSHINSKIE: Okay. So the first one we did baseline resistance studies, second we need a microbiological information packet, the third is that we need some kind of modeling and this is where we came to your point. We got to the end of yesterday saying can we model this with a small clinical trial; is it even meaningful. And that is when we got into a debate about what challenge organisms and what kind of -- you know, before and after; what are you going to look for? What are we going to dose with?

So the question is isn't that -- I think after the long discussion yesterday --- question of whether that has any utility.

DR. GILBERT: Modeling studies?

DR. KRUSHINSKIE: Yes. Or small scale modeling. Resistance modeling; resistance development modeling.

MR. RUPP: And I guess the whole crux of some of the stuff was going on -- it was my impression at least, you know, that drug companies have to put their money somewhere, and what we invest our money in has to be valuable to be able to make these decision that you need to make post-approval.

And after the conversation it was more important, at least -- and correct me if I am wrong. It was more important just to define these mechanisms, to have this information on the resistance characterization than this

modeling, because it is not going to reflect real world. If that is not what people heard -- or we would not be able to use that model to really tell us anything, that we were going to have to use surveillance post-approval. That is where I thought we were.

DR. KRUSHINSKIE: I thought there were questions about being able to validate those models and to say whether that data was then useful to extrapolate --- real world.

DR. MEVIUS: The difficulty of accreditation of the models.

DR. KRUSHINSKIE: And are they meaningful. You know, if resistance occurs very slowly through broad scale use, can you model that in a 500 bird setting or a

DR. WEBER: He modeled it in an 80 bird study. He showed whether or not there was resistance there and how multiple resistance was there, how the different drugs affected --- study.

DR. MEVIUS: But still, it is -- I also said it was a question of whether that was a valid study. We do the study. We make a lot of assumptions, and we dealt with all the questions that were brought up yesterday by Dr. White. So I didn't validate it. I saw effects. So you also have to be -- that should be a point, and I think we should mention the studies and then all the points we addressed yesterday.

And you can, because we had the discussion, also

say all the public discussions we had --- really mention that validation of the studies is essential or necessary or --

DR. KRUSHINSKIE: An area of concern.

DR. MEVIUS: Is of concern. Yes.

DR. GILBERT: Maybe if you can, under number three, we could have validated small scale resistance studies and then pull down some of our other subjects and slap it under that number three bullet.

DR. MEVIUS: And then state what are the critical points in validation. What makes it difficult to really validate it. It depends a great deal, of course, on antibiotics and --- so many different points to address.

CHAIRMAN WAGES: Okay. We are kind of stalling here. We have to do something.

DR. COPELAND: Dennis, the way we have it here now though is we are saying this is necessary, and I don't think that is what we are saying.

DR. MEVIUS: So the third point you should validate it. The result of the discussion we had yesterday.

CHAIRMAN WAGES: What did you say, Dennis, just now?

DR. COPELAND: Well, I am saying we are making a list of what pre-approval data should include, and we are saying these model studies shouldn't be part of the package, part of the pre-approval package.

MR. RUPP: And I don't think that is where we were.

DR. COPELAND: That is not what I am hearing.

DR. KRUSHINSKIE: What I am really trying to do here is just get us organized in our thoughts and then flick them off if that is not -- if we come to the conclusion that these models are not predictive of anything, then they should be removed from that list ---

DR. COPELAND: Yes. I think we need to list them and say why. That is right. So we can show them we went through the thought process and this is our conclusion. Right.

CHAIRMAN WAGES: Okay. It is 10:00. Let's take about 15 minutes. I have a check-out. And then get back here at about 10:15.

CO-CHAIRMAN GRAU: To deal with categorization?

CHAIRMAN WAGES: Yes.

(Whereupon, a brief recess was taken.)

CHAIRMAN WAGES: Okay. We are going to go ahead and get started, folks. Right, wrong or indifferent, we are going to start.

(Pause.)

CHAIRMAN WAGES: I apologize. I said you were a worrier. Don't put that in the minutes.

DR. KOTARSKI: Okay. True confessions right now.

CHAIRMAN WAGES: I make enough people mad in this

world. I don't need to go out and do it on purpose.

Would you like to give your reasoning? Hearing the conversation at the end -- and we have go to kind of, as my dad would say, fish or cut bait here and get something done. Maybe if we look at what would we like to see in pre-approval data and keep the study out of it. Okay? What would we like to see? How would we like to get that done?

And then, number three would be this is the limitations and why maybe we are not going down the right path. And if we can just agree on those three little deals, hopefully that is what was started -- and really, Jeff, I hate to say it is a futile effort on all we done. I will take pieces of this information to help me explain things, but does that look like -- I mean, we have got to do something and be -- so what do we want? The sky's the limit.

You know, whatever you guys feel is important, and then I will let you explain, Sue. B) How do we get there? And C) Is it practical and logistical to get there with current means of testing? Okay? I will sit down and moderate and shut up. Sue, do you want to go through and kind of --

DR. KOTARSKI: Okay. The material question, in terms of what we think is needed, the date would required would be -- first of all, a basic information packet. This could be a literature review.

DR. KRUSHINSKIE: See, it is on number two there.

CHAIRMAN WAGES: Yes. One other comment. And maybe even prioritize what we think is important, because when we get down to things like pathogen load or whatever, we need to still make statements that some parts are irrelevant to us. Okay.

DR. KOTARSKI: Basic information packet, which could be addressed by literature and review. And if not, you might have to provide some supplemental information. First, spectrum of activity --- zoonotic organisms; label packages; commensal organisms.

And secondly, resistance determinants that are known: Plasmid born, chromosomal mediated. You can do that in the literature review. What bacteria have these resistance determinants? What do we know? Do a literature review and find out.

And just as an information, this provides information about transferability. Notice that we are not suggesting to do resistance transfer studies.

CHAIRMAN WAGES: Okay.

DR. KOTARSKI: And second, baseline information on resistance incidence, literature review and in the field pre-approval, NARMS data. A problem with the NARMS data though. We need a more robust system to form baseline information gathering. We need a more robust system to

gather this information.

CHAIRMAN WAGES: That stems from beef up NARMS. Correct? Now, the in-field pre-approval, you are talking about going to the field? What do you mean there?

DR. KRUSHINSKIE: Is that your baseline? In what?

DR. MEVIUS: In the field. In the field. Baseline information on resistance incidence in the field.

CHAIRMAN WAGES: Okay. That is fine. Okay. I just want to understand.

DR. MEVIUS: That could be based on NARMS data or other --- studies.

DR. KOTARSKI: Okay. NARMS data. A literature review of resistance incidence and resistance in humans and animal isolates. Look through the literature. Look through the different surveys. What is the incidents that you see with the literature review in different spots of the world and the United States?

DR. WEBER: Does that include CDC information?

DR. KOTARSKI: Sure. All public information and surveillance systems. Survey of --

CHAIRMAN WAGES: Could you put that? That is perfect, to say all public information available on surveillance, both in humans and animals.

DR. KOTARSKI: Then a survey of target pathogen, which I assume we are going to do anyway. That is not in

NARMS because that is probably -- so the company would have to generate this most likely. They do this anyway.

DR. McDERMOTT: Not to be a stickler, but maybe you want to incidence/prevalence.

CHAIRMAN WAGES: Will it make us look more impressive if we say prevalence? Then we will use it.

MR. McDERMOTT: If you are talking about a brand new class of drug that hasn't been used --- have this --- background ---

CHAIRMAN WAGES: Okay. All right.

DR. KRUSHINSKIE: If you mis-use this --- we aren't going to look very good.

CHAIRMAN WAGES: Then you may want to get somebody else to present this afternoon.

MR. : All he wants is baseline really.

CHAIRMAN WAGES: Okay. Go ahead, Sue.

DR. KOTARSKI: Okay. Animal studies.

CHAIRMAN WAGES: Animal studies or animal data? You scratched out studies. Okay.

DR. KOTARSKI: Studies. Okay. Generate data on an effective dose -- on the effective dose for its impact on resistance emergence.

CHAIRMAN WAGES: Okay. Data on the effective dose for the impact on resistance emergence.

DR. KOTARSKI: Get an effective dose. If we give

that to the animals, what kind of resistance emergence do you have? Target pathogen and at least two other organisms, either commensal or zoonotic, as appropriate to the drug.

CHAIRMAN WAGES: And see if efficacy doesn't enter into this. Correct?

(Simultaneous conversation.)

CHAIRMAN WAGES: Okay. Hold it now. What? What did you say?

DR. CARNIVALE: No. I wanted to ask her how we were going to do that. Is that the model?

DR. KOTARSKI: Yesterday we said, okay, let's have an objective to evaluate the effective dose for its impact on resistance emergence. And we said, okay, that is a good objective. And then, during the course of the studies we had Paula sitting in the back the serotypes and phage types and which one are you going to use and --- sample and blah, blah, blah.

So we should be able to say to them this was a worthy objective to go for, but don't expect it to be straightforward and don't expect it to be validated, and these are the reasons why.

CHAIRMAN WAGES: Okay. My only comment is the data required we need -- it is splitting hairs, but I am going to say the data required is spectrum of activity and resistance and blah, blah, plasmid, et cetera. Not that we are going to

do a literature research and now we are going to do that. On how we are going to get that data, which is plan B. This is what we want. This is what is going to be required. This is not how I am going to get it. All right?

DR. KOTARSKI: This is not how I am going to get that. You do that for a literature review.

CHAIRMAN WAGES: I agree. But our premise -- our questions are what data do we want, period. We want mechanisms of resistance and x, y and z. Number two is how are we going to get that? We are going to get it through literature searches, NARMS data collection --

DR. KOTARSKI: Public information.

CHAIRMAN WAGES: Public information and modeling. Okay? Is that right? And then we are going to get down to the point of the practicality of -- I think where this is leading -- the modeling, pre-approval modeling to determine this and then we get to a bust.

DR. KOTARSKI: There is more than modeling.

CHAIRMAN WAGES: I know. But I am just saying that -- you all agreed that we were going to say this is the data we want, and the second thing is how would you go about getting that data. Whether we can or we can't; it is practical or impractical. C) Is it practical to do that and go that route?

DR. KRUSHINSKIE: --- is our objectives. Our

objectives is the data we want basically. That is what we need to know. The rate and extent of development. How we are going to get that data is, one, through a literature review; two, through baseline resistance information; and three, through small scale animal studies.

CHAIRMAN WAGES: Perfect.

DR. KRUSHINSKIE: Then four, --

CHAIRMAN WAGES: No. That was three.

DR. KRUSHINSKIE: Well, part three is then what are we -- Sue's point was what are we going to do.

CHAIRMAN WAGES: What are the practical aspects or the logistics of getting that data through how we would get it? Is that kind of -- Richard, help me. We have to do this. So --

DR. CARNIVALE: I guess what we are talking about a range of things that could be done. Now, within that range of things that could be done we have literature searches on the mechanisms of resistance, we have baseline collection, we have model studies and I don't know what else. And among those range of things that can be done, what are the most practical things that really should be done, and we are saying one and two are practical data collection activities.

Item three is not a practical data collection activity for these reasons. So that is what we -- I think that is what we are saying.

CHAIRMAN WAGES: Correct.

DR. LATHERS: And if the information is not in the literature, then one will have to address that data gap, if it is a needed piece of information. So I think you are talking about possible routes. You are not saying every step must always be done.

CHAIRMAN WAGES: Okay. Are we -- so the first thing is the data that we want, and the second thing is how would we get that data.

DR. KRUSHINSKIE: The objectives are --- if you were writing a --- proposal, you have your objectives, your materials and methods and not really conclusions, because conclusion will be whether there is a conclusion or not. Or whatever. But your materials and methods -- we could spend a whole another workshop debating --- methods.

CHAIRMAN WAGES: No. We are not doing that.

DR. KRUSHINSKIE: We are just identifying problems and working out those details, and it seems like information package one is straightforward. Doable. Information package two, baseline information, is doable, except that the NARMS isn't very robust. Don't expect a lot at this point in time for registration of a drug in the United States.

We would like to do that, but we can't do it unless we have a more robust NARMS sampling system so that the samples represent geographical --- the MICs that we are

seeing across the country. We don't have that right now. We are getting there, but we don't have it, and I am not sure that there is enough money to do that.

DR. CARNIVALE: But let's not discount it too much, because that is what the available system is, and that system is being used to make certain decisions and will be used by CVM to make certain decisions on trends of resistance. So it is there. It could be better, but even in its current state it is functional. So let's not throw it out too quickly.

DR. KRUSHINSKIE: Well, we probably need it, unless every company wants to --- its own.

DR. LATHERS: We do need it. And I guess the other comment is if anyone knows of data sources that maybe a university has half a collection of isolates for 10 or 20 or 30 years, we are looking for those information as well to help all of us to beef up, as you would say, the NARMS.

CHAIRMAN WAGES: Okay. So we have got our data baseline information packets and public information on resistance, NARMS, et cetera; surveillance. Then we go to animal studies.

DR. McDERMOTT: Maybe you should just take out animal studies, because --- varied data on ---

CHAIRMAN WAGES: See, that is what I was going to do. I was going to say we need data on the information, and we can get these through literature searches, you know, pilot

studies; whatever.

And then, after we list the possibilities of collecting that data, the practical and logistical ways to get that data is based on literature searches, baseline resistance from known surveillance or public availability of surveillance data, both in human and animal; however, on the animal studies, hopefully there will be a list of criteria; why those won't be appropriate for pre-approval data collection. Is that what we want to say? Yes?

MR. RUPP: That is what I would like us to say.

DR. BUTLER: Kelly Butler, Health Canada. I would suggest, in terms of mechanisms of antibiotic resistance, that the people who know that best are the sponsors of the drug. They know that from having the drug around for 10 or 12 years; that that is inherently a piece of knowledge that the sponsor has. So that makes the next step of possible studies -- you narrow things down pretty sharply.

CHAIRMAN WAGES: Yes.

DR. WEBER: I want to keep in mind the sort of things -- I think we are going to go back to the center in looking at these pieces, this information, these suggestions. The overriding sense in my mind -- and I haven't been part of these decisions up to this point, or these discussions.

The clear thing in my mind is the fact that we will be able -- there has been identified a concern for microbial

resistance, and we have to include that in this approval and existent study of drugs. In that knowledge we can bring to bear information on a new drug and that background will affect its approvability obviously, but even more so perhaps on its remaining approvable.

CHAIRMAN WAGES: Its livability.

DR. WEBER: And again, to say that we don't know anything or we can't provide anything, other than a little snippet here and there, really will limit our ability to deal with this in a management decision. To me that is clear.

If we only have information on human resistance and you see it go up, and we don't know anything about amelioration effects, profiles, you know, resistance determinants that might be emerging here or there, the less information we have that has been provided or can be gathered, the less our ability to do anything other than perhaps the worst, and we don't want to go down to that.

CHAIRMAN WAGES: Okay, Nick. Are you saying that we are not providing that here?

DR. WEBER: I am seeing -- for the last couple of hours -- that the trend is to say, well, we can't do that, we can't do that; we are not going to provide data; this would be nice to have, but it is going to be too hard to go. I am just saying the less and less information you think you are going to provide or will be useful to provide will impact on

our ability to have an information base to make further decisions.

CHAIRMAN WAGES: I think that point is well taken.

DR. LATHERS: I think it is very important that we realize that there is a public health issue being raised today on the human side, and they, in turn, are pointing the finger perhaps at animal drug usage in terms of antibiotics, whether it is feed or whether it is therapeutic.

We know that there are questions that should be raised about the appropriate use of antibiotics in humans, and it is not as if the community has absolved themselves of any problem. But our responsibility in developing new drugs for animals and/or food animals is to provide a baseline data so that we do understand what we are working with and can defend the use of these particular agents.

And so, any piece of pre-approval data that can be provided to strengthen the arguments to keep that product on the market is what you need to do.

CHAIRMAN WAGES: Any pre-approval information that would add to --

DR. LATHERS: Our knowledge base.

CHAIRMAN WAGES: Yes. For post-approval decision-making.

DR. LATHERS: That is right.

CHAIRMAN WAGES: Now, the other thing that someone

brought up -- this is not my idea. Let's not get bogged down in a study that is difficult to validate versus a pain in the butt to do and we don't want to do. Don't quote that. But, you know, what I am saying is just because something is difficult to do, from a logistic -- you know, from -- I am not saying this right.

Just because it is hard and it may require some thinking of this outside of the box to get something, an answer, I don't think should preclude us from doing that study. That may open a can of wax, but let's don't confuse the two of being that is just hard to do and we don't want to mess with it, versus it can't be validated and reproduced, period. Or something like that. See what I am saying? No? Maybe?

DR. MEVIUS: I agree with you. You shouldn't hide behind problems in a study and then we don't want to do it, but with animal models, validation of such a study may never be possible. But that doesn't mean you can't do a well designed study that has -- well, some predictive value. Really, validation is -- well, we talked about it in the coffee break. That is --- work, and you won't be able to do that for such a study.

For instance, if we could say that for category two drugs, this kind of information is available, this should be at least enough. And for category one drugs, at least an

attempt should be made in animal studies, well designed, to show the effect of the effective dosage on selected bacteria.

CHAIRMAN WAGES: Okay. There was another hand up. Richard, you were --

DR. CARNIVALE: No, I didn't.

CHAIRMAN WAGES: That one eyebrow is up.

DR. CARNIVALE: I'm sick.

CHAIRMAN WAGES: I am too, but not in the same way.

(Laughter.)

CHAIRMAN WAGES: Okay. We are at animal studies. Correct?

DR. KOTARSKI: Do we agree with one and two?

CHAIRMAN WAGES: And I think I am going to put a little -- the caveat saying that any information that can be provided through reasonable means, pre-approval, is going to add to the potential for effective post-approval monitoring. Something like that. Boy, that sounded good.

And then, try to put that in a broad -- I think we agree with that. And that would capture, I think, some of the things we are talking about.

Now to the animal studies, which we are having problems with. That is, a way that we can get data, albeit it has been defined or described, if what I am hearing is correct, as difficult; not practical. All sorts of words to come into it. How do we want to tackle the animal studies?

DR. KOTARSKI: First of all, the objective in animal studies?

CHAIRMAN WAGES: What is the objectives?

DR. KOTARSKI: What is the objective of the animal studies?

DR. KRUSHINSKIE: Just to collect more data.

DR. KOTARSKI: The objective is to collect more data?

(Simultaneous conversation.)

CHAIRMAN WAGES: Originally the studies were trying to be predictive on some kind of --

DR. WEBER: On rate and extent.

DR. KOTARSKI: The objective is to acquire data on the impact of the effective dose on resistance emergence, rate and extent. Right? I'm asking.

MR. RUPP: Where do you stop it? Do I start my animal study and to what extent?

DR. BUTLER: Can we say clearly that the sponsor is aware of the antimicrobial resistance mechanisms because they have been with the drug for 10 years or 12 years. They know that. And so, when you go from that knowledge base, which is pretty key, then you can focus into the extent; whether or not there is cross resistance at various doses. I mean, you have that knowledge.

DR. KRUSHINSKIE: I think in item number one that

information is in that.

DR. BUTLER: Well, saying literature review or -- yes. Okay. So you are giving that information at this time, that you see the antimicrobial resistance mechanism is such and such?

DR. KRUSHINSKIE: Right. Right.

DR. BUTLER: So, if you go from that, then that makes it a narrower piece of information to go after?

DR. KRUSHINSKIE: Yes. And that is what is in that first packet. Number one is the microbiology information packet, the literature, everything you know about the organism; mechanism of action, resistance -- known resistance mechanisms, et cetera. Anything known is collected.

DR. WEBER: That makes the design of the model relative to your projected efficacy. Dose and duration.

DR. KRUSHINSKIE: The impact on non-target species.

DR. WEBER: Right.

DR. KRUSHINSKIE: --- question on whether that can be realistically modeled and be meaningful. And my question --- we talked about yesterday is if it shows --- study, go ahead and give them the drug "x" and resistance develops to drug "x", what happens then? I mean, it is going to happen because of --

DR. BUTLER: Mitigation. Alteration of doses. What would you -- I mean, you are the experts. Do you change

the doses and how does that mitigate the outcome?

DR. KRUSHINSKIE: What does that do to your target -- your efficacy for the target organism that you are actually trying to get licensed for? So that is a whole can of worms on that.

MR. RUPP: If there is no human health impact, I probably wouldn't do anything.

DR. MEVIUS: If there is no human health impact, it wouldn't be a category one, and probably, it is not relevant to do that kind of study. You should do it for the extra information for the relevant human health impact drugs, and then how, to deal with the information. Your point you just made. That is very, very difficult.

CHAIRMAN WAGES: I think what you were saying, at least in my mind -- what is the extent? What bug do you use? What serotype do you -- that would be in explaining the problems associated with the potential designing of a good descriptive model that would answer these questions, and I think that is -- I am not saying you can't do it.

I am saying that that is the problems we identified. What Paula said yesterday that may be involved in getting a nice predictive model of resistance.

DR. WEBER: But with that knowledge you can go forward and say I am not going to use this salmonella. I am going to use that salmonella knowing this. With that base

knowledge -- and that is what Dr. Butler was mentioning.

With that knowledge base you do the best you can. You come in and you work out those protocols. You wouldn't take one that is resistant or this, that and the other thing. You come to an agreement or understanding about what is the limitations and the practicability of these outcomes and use your knowledge to design them.

DR. KRUSHINSKIE: I think my biggest concern with this portion of it -- maybe --

DR. WEBER: This is what the whole workshop was about, is looking at the design of these studies.

DR. KRUSHINSKIE: This one animal model. When we look at baseline studies, that is a crap sheet of what is out there. We don't have control over what is out there. Whether it is good or bad news, it is not any choices we make. We are just going to survey it.

But when we get to this study, depending on what the magnitude or the consequences are to the results from this study, we have a tremendous risk involved in picking all the factors that are going into the study design because of the consequence of the outcome. And we don't know what the consequences of the outcome are today.

We don't know if it means -- if it goes up, you can't be approved and that is the end of the story. Or it means, oh, it went up. We are going to watch it. That is a

piece of information to use later on. And that is another question, pivotal versus non-pivotal. It comes in and it makes those decisions on which bug you pick, how you set the trial up, what age bird do you use, et cetera. Extremely critical, because a miscalculation in any of those choices, you shoot yourself in the foot.

And I think that is the concern of everyone here, is we don't know enough about the ramifications and consequences of these trials. We don't have prior trial experience to have any kind of basis to say, well, I think that this is -- we have done this before and this model has worked.

DR. CALVERT: But in the absence of that information, you shoot yourself in the foot also.

DR. KRUSHINSKIE: I know. We need to work through it. But that is the anxiety. That is where the whole problem is.

CHAIRMAN WAGES: Nobody could have sat and listened to the meeting yesterday -- however many days we have been here -- and came out of there and says, well, these pre-approval studies and modeling for this predictive is -- guys, this is all right. This is good. There is no way. Nobody was positive about it.

And I don't think CVM brought in the negative aspects. They said, here is all the potential problems

involved. I am not convinced, Nick, that we can sit down here and say that we can design models too to do it.

DR. WEBER: We are just saying -- let's try to work through this, because what I am saying, what we know for a fact, is that without them, without some knowledge base to approve the next antibiotic, it ain't going to happen. They are telling us now.

We need this part of our human food safety evaluation. So work with us to develop scientifically placed useful information and let's use it as best we can to go through to an approval.

DR. CALVERT: I don't think anybody is not saying that, Nick. I think we are saying that one and two are useful information upon which to base a decision whether to approve the drug or not. But the real issue is how that drug performs on the post-approval side.

So doing these predictive models, you know, may or may not be practical two years, five years, 10 years down the road as more information is found, but the dose kinds of model studies are just not going to tell you very much about what is going to happen with that drug once it gets out in the marketplace.

And you can design any study you want and you can set any criteria you want and check the box and say we did, but, in fact, it is probably not -- for all the reasons that

we talked about yesterday, it is probably not real relevant to the real world situation, which will only be known when the drug goes out on the market.

MR. : Why should we take that chance?

MR. : You are not taking a chance. What chance are you taking? You are collecting all this data. You are looking at baseline information, you are looking at the mechanism of resistance. You have gone through massive efficacy testing, you have set it under prescription use, you have limited the label, you have got a post-approval NARMS program in place. What chance are you taking?

I mean, what exactly is CVM worried about? If you are worried about resistance occurring after the drug gets on the market, then you might as well say, we will never approve another drug. I mean, I don't get it. That is what I don't understand. What are you worried about before the approval? What is it that you need to tell you before you approve this drug? That it will never cause resistance? I don't think the industry could ever say that.

CHAIRMAN WAGES: And I will say one thing, and then I will call -- what I find troubling is let's say we predict the resistance in this antimicrobial to be -- this is going to be a very long-term -- a lot of use and the resistance is going to be very slow going. We said that about fluoroquinolones originally back years ago at the VMAC

original meetings.

And the post-approval monitoring in one year out sees this extremely high risk in resistance. It doesn't matter what this predictive model said pre-approval. So why not have the focus be on what happens with the information we have about its mechanisms of resistance, about its use and categorizing for importance in humans and put your money into stringent post-approval monitoring and react.

That is what is going to determine -- not that we predict -- I mean, maybe if we predicted in one month we are going to have resistance it never would be approved. But if it predicted whatever it said, if post-approval shows the resistance problem occurring in humans, there is going to be some kind of mitigation. It doesn't matter what happened pre-approval.

Put your money in the post-approval so you can react. Thank you. You can quote me on that one.

DR. MEVIUS: I would like to respond to you. You bring it out as if you can't control resistance. You say this baseline data are going to give you all the information and then you license a drug and then you are going to check afterwards what is going on, which you will have to do anyhow.

But the basic thing is that you can control it, and you can control it in the way -- how use an antibiotic, and

that is not only how you -- the dosage -- the way you design the dosage and how much you administer to the animal and how long you administer to the animal, those are really critical points.

So if you are in these kind of animal studies for these chronic health --- antibiotics you can find a certain dosage --- in these models --- very valuable information. Not only for CVM, but also for the industry and for the veterinarians; for anybody. So it is in everybody's interest to do that.

We all want to have rational therapy, but if we can improve those regiments, yes, you can control the problem. The problem will arise anyhow, but we need to control it; otherwise, we can ban all antibiotics, and we don't want that.

CO-CHAIRMAN GRAU: Let me just interrupt. Do you want to continue in the direction where we are moving with Susan and then come back to this, this part of the conversation about the need for pre-approval studies, the robustness of them versus post-approval? Should we just table this for just a few minutes so that we can complete this aspect. I am saying that I know -- I am drawing a distinction between the two. That may not be accurate.

But do you want to just finish this conversation? Why don't we start here with the flip chart and then come

back to this conversation so then we can have a statement about pre-approval studies, their usefulness, their potential usefulness, versus post-approval considerations. Can we do that? Because it is great conversation, and we can continue it until noon, but we will have not have anything that we want to report back to the larger group.

Okay. Susan, do you want to -- I know you are writing some other things, and I am not sure we were complete with number three.

DR. KOTARSKI: I was just trying to record what I was hearing. But I would say that -- ask if people want to use just those three; that they agree at least to those three as capturing some of the ideas that we had yesterday and today. Your first question was the data that is needed pre-approval. Right?

CHAIRMAN WAGES: Correct.

DR. KOTARSKI: Okay. So the first package -- data that we want: Package on rate and extent and resistance emergence. How do we get this? We have three aspects of getting this. Number one is an information package about resistance mechanisms, spectrum of activity, and this can be gotten both by public information, information that maybe the sponsoring has in human medicine or whatever, because we have private information.

Information about resistance determinants that are

know, whether they are plasmid mediated, chromosomally mediated, what bacteria have these resistance determinants. We all agree that that is practicable and doable.

Number two is baseline information on resistance prevalence. Surveys that are done in-field pre-approval would be one of getting that information. A second way of gathering that information is using a NARMS information database. We would like to see more robust systems. We do support the system. Right? Okay.

A literature review of prevalence in human isolates, animal isolates. Maybe we have some surveys within our companies. But public information, sponsor information, if there is additional, and a survey of target pathogens. And likely, we will have to assemble that information as an active --

CHAIRMAN WAGES: Okay. And -- go ahead.

DR. KOTARSKI: Okay. A third way to address the data package that we want is animal studies. We want a well designed animal study. At least one I guess. This is where we -- you know, it is not as clear cut. We are thinking in terms of the objective of this study to provide a well designed study that allows us to acquire data on the impact of the effective dose on resistance emergence; rate and extent in the target pathogen, and if we can, at least two organisms, commensals or zoonotics, as appropriate to the

drug.

There is some problems that we have identified to do this study, and that is found on page four of the Word document. Or it was page four.

Those challenges are that salmonella --- resistance emergence in salmonella. Salmonella doesn't have a high prevalence in birds. So then you are relegated to a situation, if you want to look at resistance emergence in salmonella, to thinking about challenge dose studies.

And then we ran into the problem, if we wanted to use challenge dose studies, what salmonella serotype do you look for and --

CHAIRMAN WAGES: We had those captured, those comments from yesterday.

(Simultaneous conversation.)

DR. KOTARSKI: And when we talked about salmonella, then we realized that the same challenges apply to camplyobacter in designing these studies. The other thing is that we are designing these studies, so we have a lot of uncertainty as to whether or not they have predictive value. We know that we might want to do some replications. And now I am getting at the end of my understanding, and I will take it over to the group.

CHAIRMAN WAGES: I think you did real good.

DR. KRUSHINSKIE: Just one technical change.

Salmonella is not prevalent in birds. What is prevalent in birds --- so I don't think I would say that.

CHAIRMAN WAGES: Well, the prevalence of salmonella versus -- we know it has got to be 20 percent or less in a plant.

DR. KRUSHINSKIE: I'd say it is low.

CHAIRMAN WAGES: Yes. We want to be careful not to paint ourselves a pretty picture that we don't have. Does that give us the -- I think I will try to emphasize we think there is -- there would be importance to these studies, but the problem is designing one. And maybe that is for the future. Maybe that is for research and maybe that is for a direction at some point in time to look at a predictive model that could be validated and could be used in the pre-approval process.

I don't think we want to send a message that, you know, we don't think it can ever be done. I mean, if we could find some way that a model could be satisfied and be predictive for us, I think that would be great. Our problems with them is -- at least the experts in this room says they are not predictive based on the problems designing, et cetera. Dennis, you had your hand up. Go ahead.

DR. COPELAND: It still goes back to what I brought up yesterday. Let's assume we could design a perfect model that would be predictive. How would that information be

used? What would you do with it? How does that help make a decision on approving the product? Or how does that help make a decision after approval if you have a robust monitoring program and that is what you are using for regulatory purposes?

I am just struggling with how you use this information.

DR. McDERMOTT: I think this is exactly the point where we are straggling the two issues that David brought up. Here we are doing studies in animals to look at the best dose to minimize resistance, and if we could just simply --- that is a good thing. So we have got an effective dose in light of this resistance. We are not at the predictive model yet.

All we are saying is, okay, that would be a good piece of information to know, and then we go to the whole question about is this data going to be most useful for pre or post-approval. So we are not looking at predictability at this point. We are just looking at optimal dose.

CHAIRMAN WAGES: See, I thought we were trying to predict the incidence and the rate of resistance.

DR. McDERMOTT: Not in dosing optimization. My understanding is you are trying to find the optimal dose to minimize resistance in that animal. That is a different set of animal studies than trying to predict what is going to

happen post-approval. Isn't this where the two issues intersect?

DR. COPELAND: Well, I thought Sue -- you know, Sue brought this up yesterday. Are we looking at a different way of selecting dose now? And I thought we went through that discussion and decided no; that we are still going to select the dose for the target organism. It would be nice to know what impact that has on commensal organisms.

But if you are going to start selecting your dose based on zoonotic organisms, that is a whole different issue.

MR. : You can't do that.

CHAIRMAN WAGES: It would be nice to marry the two where you would have an effective dose that minimized resistance, but -- and that would be things that you would do. But I don't think you could base your dosage on strictly zoonotic.

DR. KOTARSKI: What if you approached it from a different way? You said, I found an effective dose. Here it is. And I do or do not see resistance emergence. Because, if you have a new drug or whatever, maybe you don't see resistance emergence in that course of therapy.

So, if you don't see resistance emergence, you say, well, if you use it in this way, you help the judicious use principles to say if you use it in this way or if you use it within the flexible labeling, you know, within this range of

dosing, then we have some data to suggest that you won't see resistance emergence. I mean, we made a good faith effort to say that or to have data to support that.

On the other hand, if you do get some sort of statistically relevant resistance emergence, you say, well, I modulated my effective dose and it is or is not the same when I modulate that dose.

DR. CARNIVALE: Are you talking about target pathogen?

DR. KOTARSKI: Well, target pathogen and the other pathogens.

DR. CARNIVALE: But how are you going to do the other pathogens?

DR. KOTARSKI: Just a couple. Well, yes.

DR. CARNIVALE: That is the problem here. You are modeling your effective dose on the disease you are trying to treat. That is what the company gears their dose towards, the pathogen that they are looking at. So obviously they are doing their dose titration studies or whatever they are doing, PK models, to look at that target pathogen, and they will do their efficacy studies and obviously test the susceptibility of that pathogen and look at it pre and post and determine whether there is any resistance emergence in that target pathogen.

But then you are adding another conundrum. How do

you do that study, adding the salmonella or the camplyobacter to it? That is where you really run into problems.

DR. KOTARSKI: Right. And that is the conundrum that should be a bullet point on the -- from this committee, the fact that we have gone through and, you know, thought about those things, and here is the problems you come up with. You say, okay, I am going to do that, but then I have to challenge with these other organisms and then I confound my objective and my ability to achieve my objectives.

DR. CARNIVALE: But can't you also satisfy the effective dose issue by knowing what your effective dose is against the target pathogen and then looking at maybe concentrations in the intestinal tract and how that relates to the MICs of various group one pathogens to kind of get an idea of, if you do treat for a --- disease and you have certain concentrations in the gut, you know that it is going to be either above or below certain MICs of food-borne pathogens.

DR. KOTARSKI: It doesn't tell you any --

DR. CARNIVALE: Well, I mean, at least it is some information.

DR. KOTARSKI: No. It won't unfortunately.

DR. KRUSHINSKIE: Can I ask a question of CVM? Once you go through this information and you get all the information that is presented in packet one, you get baseline

resistance information, don't you think you really have at that point a really pretty good idea of whether this is a suitable product or not?

DR. LATHERS: In safety and efficacy is where we begin, of course, for animal, human and the environment. But then the sub-question that comes up is that rate and extent of development of resistance to those products, antibiotics, that are of supreme use for humans, and that is the balance.

DR. KRUSHINSKIE: But if you are getting resistance information, realigning the database, the knowledge base of every other work that has ever done on a product that is similar or a similar mechanism, I would think, by the time we get all that information, you are going to have 95 percent of what you need to make your decision.

DR. LATHERS: For the pre-approval process.

DR. KRUSHINSKIE: For the pre-approval. And this study is maybe a piece of it, but it is not really going to be adding that much more to it.

DR. LATHERS: I think what you are almost concluding is that some of the information that the company will have in that 10 to 12 year development period about the emergence of resistance and cross resistance will become part of the database that then -- post-approval in terms of monitoring.

I think we all have to realize that it is the

global use of antibiotics, where if you want to think of the world as the stage and the use of the drugs as they wax and wain both in humans and perhaps even as we use them in animals, maybe something that we can do in some cases is to withdraw the use of the drug temporarily in animals and then, you know, re-initiate it as that occurs.

So I think it is the bigger picture that we are working on. So yes. We hope to have something for the pre-approval aspect, but we are going to -- you are going to be providing a database then that will help us and you understand the use of your drug post-approval, in terms of safety for humans. And that is the problem.

CHAIRMAN WAGES: Okay. We have to do something here, folks.

DR. BUTLER: Can I just add one little -- I really that point, Claire. If the information that you gave in this case said, well, we know with this particular drug there is cross resistance, then where are you? I guess that is where we are looking for this model.

If you know that there is cross resistance in this very closely related drug and you have got a new drug coming forward, then it would benefit you, this is the point, to say, okay, well, here in our package number one it shows this, but, by the way, we ran this study on these three bugs and we said, here are our results. We did not see cross

resistance to this other important drug developed.

That is kind of the bottom line. So if you could -- I am just speculating for our system; that if you could tell me that, then that would be a really big plus in terms of saying, well, they did this study, they recognize it is related to this one, but with this information I can see it doesn't have an impact. Then you have to look at the post-approval process.

CHAIRMAN WAGES: We had a comment about that on CVM needs to be flexible and allow company sponsors to develop -- or be able to provide information to -- we said alter or change or move the categorization of a drug based on exposure. Something like that.

DR. KRUSHINSKIE: Well, I guess the point I am trying to get to here is we are spending a lot of time on number three worrying a lot about it, because by the time you -- really, by the time you get to number three, 95 percent of the decision making process of information you need probably is already there, and it is only going to be in those cases where it is questionable, it either has a lot of resistance or, you know, there is something about it that is unknown where this study is going to give you additional information.

DR. WEBER: Just list the difficulties that you, as an industry, have with it. We are here to listen. We are

not here to have to debate this all the way for the next hour. That is not our objective here. If you think it is not going to be useful, list the things that is not predictive. You have got a bunch of this thrown out through here. We are listening. We are here.

You are not going to get decisions at this meeting today that we are not going to require these studies. That is not the objective. We are trying to see what kind of information this data might provide. As we point out, it might be useful. If we believe it is going to be useful in other mitigation -- at least trying to understand the product so we have some basis for future regulatory actions other than just withdraw because we don't know anything.

CO-CHAIRMAN GRAU: Do you want to capture that? Does the group want to capture that? Do you all want to capture what you just said about 95 percent of the information is within one and two and so it speaks to the need --

DR. KRUSHINSKIE: I am trying to need to put this in perspective with the rest of information. It is probably a relatively small piece of the package in the end of the day. I am saying not get so wrapped up in it.

CO-CHAIRMAN GRAU: Right. Does this group want to make that point?

DR. COPELAND: Would you want to word it as a

question? Does this kind of study add significant additional information that would help the agency in any way?

DR. LATHERS: And the industry.

DR. COPELAND: And the industry. Right.

MR. RUPP: What is our answer? I mean, that is why we are here, to pose these questions and address them. Do we have a recommendation to that answer? I mean, I don't think this is just a forum, Nick, for industry to debate things or whatever.

I think this was the forum in which we wanted to try to put some proposals -- both CVM, industry and interested parties; some answers to these questions. So I think it is a fair question, but now it is -- you know, what, as a group, do we want to put down for our answer?

DR. LATHERS: All right. So you pose the question, and I guess another question that compliments it is, is there a type of study that could be designed that would give you a hint as to the rate of resistance development and couple that with how it will either impact the antibiotic use in the animal industry or in the human industry. And in some cases the human side may not even be a question. So then you are just focusing is going to impact its use on the animal industry.

But if it does impact in humans, what piece of information do you need? And now you are talking rate of

development of resistance. What type of experiment, if any.

CO-CHAIRMAN GRAU: Does what Jeff have -- Jeff wrote question of practicality and then most information gathered under one and two will allow a decision on approval to be made. Is that --

DR. COPELAND: I thought I heard practicality as one issue, but also usefulness of the data as another.

CHAIRMAN WAGES: And value.

DR. KRUSHINSKIE: I don't think practicality is the right word, because it is not whether it is practical or not, but -- my intuitive feeling is you are going to pretty well have a pretty good idea of whether this drug is dangerous or not or a safety problem from a resistance viewpoint by the time you gather all that other information.

So my question is, really, how much value does it add? Is it five percent? Is it 50 percent? Is it equally weighted? Is it just as important as item number two? Or is a little piece?

DR. WEBER: Do you really think we can answer all those, whether this is five percent or 95 percent?

DR. KRUSHINSKIE: No. But just think about it.

DR. WEBER: I am just saying we have spent a huge amount of time on these policy issues, and, as far as I know, don't look for me to give you that answer. I haven't been given that meeting yet as a center director, and I don't even

know if I am going to get invited to that meeting. I am not going to answer that question for you.

And the fact that I am not throwing a bigger rock at this only -- I am just going to just be neutral about it, because I am just here to ---

CO-CHAIRMAN GRAU: Okay. Is that now question of the value of the data from number three, the animal studies, relative to the information that will be gathered in one and two?

CHAIRMAN WAGES: Yes.

MR. : I have a question. We know that -- and maybe, Nick or Claire, you could maybe give us a little insight on it or guidance.

We know that some sponsors are proceeding on one-on-one as we go through for development of some of these other products. It could be in poultry, it could be in whatever, --- et cetera.

CHAIRMAN WAGES: I doubt it.

MR. : Pardon?

CHAIRMAN WAGES: I doubt if it is in poultry.

MR. : And so, as these sponsors are going through, one thing that we heard is, well, you need to do a pre-approval study that will be used in some manner. I guess the question then is, given the expertise and the experience of the agency thus far in dealing with one, two or whatever,

what have you found out thus far in requiring these pre-approval studies for some of these newer drugs?

Have they been useful? Do you have any information or insight as to how you are using them?

DR. LATHERS: In terms of a generic answer, Jeff, can you make a comment?

DR. GILBERT: As generic as possible, I would say that indeed people are proceeding with antimicrobial development; however, I am unaware of any study that has been conducted so far. I haven't seen anything for review.

DR. LATHERS: But you are working on protocol within the --

DR. GILBERT: We have looked at protocols. Yes.

MR. : So the question is -- you know, we are all of different opinion as to the value, and obviously right now, if I am sitting in a reviewer's chair, I am thinking I need some further data. And so maybe, if we put you in the chair, you can say, all right, what am I looking for, and as I review protocols, what do I hope to gain?

And maybe that will help us get a little better feel for what the value is and maybe how they should be designed or what the scope might be.

DR. GILBERT: Based on my concerns as a reviewer and knowing what influences are crashing down around me all the time and why, you know, the focus on me, I think we are

looking for some assurance that whatever drug gets unleased on the market is not going to adversely effect the public health.

If resistance emerges rapidly, we might say this is too fast, especially if it -- let's say it is a fluoroquinolone and you put it in either a challenge model or you just look at the base floor in an animal, treat it and come back later and all the bacteria you pull out of there is just as resistant as it can be. That is, you know, a flashing light, and I know that surveillance and compliance -- that arm may then say no, this is not good.

We would recommend to Dr. Sundlof that you not approve this. Despite if I can get Claire to sign off on the letter, there are other forces at work that may so, no, there is too much information there.

Or, if I got the study and it looked clean, no matter how much drug you threw at it, it had the same effect on the bacteria, that is a big check mark. I can rest assured and the microbial safety package or portion of the human safety package is okay.

MR. : And the safety net then, from a reviewer's perspective like you say, is I don't see a real trend developing in the pre-approval study, so that is a big check mark. My safety net is the NARMS and post-approval.

DR. GILBERT: Right. As Dennis pointed out, we

could approve it, and within a week or two resistance -- you know, no matter what the study said, at least I had some information there to tell me. I didn't just pull the answer out of my head. You know, there was something concrete there that I could say that I reviewed this information and it looked okay. This is the best shot at the time I wrote that approval letter.

After that, everything is off the table, and that is the way it is with all drugs. You know, you find out some are real nasty when you get it out there. You get all sorts of adverse effects. We can't predict for everything, but we have to have something to chew on.

And we have looked at some protocols, and I did not -- you know, intentionally we did not want to bias the audience saying what we have looked at. We thought maybe somebody would come up with an angle that we haven't even considered; a mathematical model, PK/PD data, and I haven't heard anything yet to tell me there is anything new that we missed.

But I have heard a lot of -- that some of the things we have considered may not be practical. So we are going to have to consider everything that you have told us. It has been very good information.

But I think, this is, again, your opportunity to tell us what you think would be the best way to satisfy our

concerns.

DR. COPELAND: That is what we have been driving at, is how is this information -- how would it be used? That adds some clarity. It is still not real clear, but --

DR. GILBERT: There is going to be a decision. It is not going to be just mine. A lot of people are going to get together and say, you know, look at this data. It is real fuzzy. Can we draw something from here? It sort of induces resistance, it sort of -- we do that every day with every drug we deal with. But I think there will be a regulatory --

DR. COPELAND: I just hope you can see why there is some hesitation here, because, having said that -- and we are correct, that it is going to be very difficult to run a study that is predictive, then that study could come back and bite us. It could prevent us from getting on the market when we should be on the market. It may allow us to get on the market when we shouldn't be on the market.

DR. GILBERT: What about --

DR. COPELAND: That is the purpose.

DR. GILBERT: What if your talk study fails? That would keep you off the market.

DR. COPELAND: Sure.

DR. GILBERT: Okay. This is where we are at. This is a newly arisen human safety -- you know, it is a big deal

now, and it is as bad, you know, --- we have to address it.

CHAIRMAN WAGES: Okay. We are going to get going here. Go ahead.

DR. LATHERS: I would just make one other point. I think the center is looking at the questions and we are trying to determine the policy in terms of the regulatory actions as well. Take the concept of the threshold. Is it valid or not?

Is a pre-approval study independent of that threshold concept? Or is there a greater role for post-approval threshold and what do you do? Does that threshold, post-approval, become first the warning bell that the rate of resistance is changing and the, finally, the human side is compromised, so therefore, we cease and desist in the animal industry? These are questions that we don't know.

Can we establish a threshold data? We are not sure either. We are looking for answers and trying to formulate them as well as to what to do with the data. This is your chance to give us your best input.

CHAIRMAN WAGES: Okay. Well, we have 30 minutes to figure out how we are going to do this this afternoon at 1:00. Our premise, just to summarize how we would like to -- what our objective is in the data, how would we go about collecting it, and then, in the animal studies, go ahead and

go and explain some of the concerns surrounding those studies. So we are okay with that.

Then my other question, my last question, would be -- and then we said we would come down to the nitty-gritty of are pre-approval studies necessary.

But I would say can we get the same information that we want, that we desire, in another ways? Are there other information gathering or data collection or whatever procedures out there that we can use to answer our questions? To predict resistance, to --

CO-CHAIRMAN GRAU: Out there or not out there.

CHAIRMAN WAGES: Out there or not out there. Thank you. Let's go with if you had to design it yourself and tried to go tot he agency and say, okay, this is the information I got and I think this will allow you to make an informed decision about the possibility of this occurring and being a human health hazard, resistance, x, y or z -- now is the time to say what is important. This is the post-approval monitoring. What is it?

(No response.)

CHAIRMAN WAGES: Okay. With no information, we are adjourned. This was a big issue yesterday, and we said we would come down to the nitty-gritty of the pre-approval.

DR. WEBER: I haven't made a survey here, but I know there are -- I believe there are at least three card

carrying microbiologists here. The rest of us are regulatory or policy or something like that. So I am hoping for some direction from them before we jump on it from a policy or a regulatory standpoint. Let's start with the science part of it.

CHAIRMAN WAGES: If it pleases you, it tickles me to death. Sir?

DR. WEBER: Oh, there is four.

CHAIRMAN WAGES: Could you state your name?

DR. SAGRIPANTI: Sagripanti, Center for --- FDA.

CHAIRMAN WAGES: Okay.

DR. SAGRIPANTI: I think that what has been the big struggle for this group, but for others, is this attempt to get an absolute number for risk or bacteria resistance in an absolute number, and that -- you know, everybody is bringing like 100 variables and 100 unknowns and a big thing.

What I would pose as a question with what is presented there is what if, instead of attempting to give an absolute number for that risk, --- compare it to in relationship to some -- I don't know if the state of the science is enough for each particular application, but if it would be enough, one can just request something and compare it to something, which is either bad and then it is much better or not. It brings imbedded with it the concept of threshold. Perhaps.

If you were asking how would you do it, I would do it in just a relative way in which some conditions would be set as standard. They may not be 100 percent perfect, but they would be 80 percent; better than nothing and will give you an idea of how that compared to something else. Fluoroquinolones and camplyobacter or whatever.

And if the thing is obviously as bad or worse, then you have your, you know, confidence in your selection. If the thing seems to be passing with flying colors, then you have a relative assurance that the thing is maybe not as bad as expected.

That would make life very easy for the reviewer, it probably would make life very easy for the sponsor, and again, it is not a 100 percent solution, but maybe an 80 percent solution that people perhaps can live with. I am just posing it as a question.

CHAIRMAN WAGES: So you are looking at not absolute numbers. A trend that could be established; that we were here at this baseline and a month or a year later we are here, and at what threshold is it bad.

DR. SAGRIPANTI: I would even go to the pre-approval stage in which all these experiments that would be done would be run with a standard. Call it silver standard -- and then just a comparison. You know, if a standard can be selected, which is what I don't know. But if you could,

then you just get a practical way of going around --- enough --- can be determined.

CHAIRMAN WAGES: Paula?

DR. FEDORKA-CRAY: Well, from a microbiological standpoint it is -- you know, how do you select that? I mean, that was a question we were just talking about in another group. How do you select that organism? Because you have this strain and you have the serotype and a phage type and a species, and is it really going to give you -- it is just going to give you a view of what is happening in that particular strain. You know what I mean?

Resistance to one antibiotic is just that. Resistance to one antibiotic in that particular bacteria that you are looking at. And while you can say that there is some -- you know, you can probably say that you are -- jejuni -- you know, you can look in there. You know, you can just say, okay, all jejuni.

But you have to do some looking ahead of time to know if that is a valid statement, and my concern would be how do you set up these studies and who has the burden of setting up those kinds of studies to look at all of those different organisms, you know. And then selecting one. Who is going to do that? And is it going to be enough, when it finally comes down to it, to come and say -- and it changes. It will probably change for every drug. So you have to have

a whole battery then.

DR. SAGRIPANTI: We are selecting them now. We are selecting them now for any kind of claim that is presented in any application.

DR. FEDORKA-CRAY: Well, I think that the only claim is on the target pathogen.

CHAIRMAN WAGES: The dose is not put on there to minimize resistance or transfer resistance to a zoonotic pathogen. It is to nail E. coli. and air sack in broilers, period. Now, that is the history, and now maybe what people are saying we need to shift that. But that is what the dose is.

I don't know much about it, but that I do know, that the dose is based on the target pathogen in the species, period.

DR. KRUSHINSKIE: But you can't compromise that.

CHAIRMAN WAGES: Right.

DR. KRUSHINSKIE: What is the point of having the drug? If we are going to set it up to not induce resistance in camplyobacter and it doesn't work against E. coli anymore, then what is the point of it?

CHAIRMAN WAGES: Well, I think they are talking about marrying the two, and --

(Simultaneous conversation.)

CHAIRMAN WAGES: Correct. Is that a viable option,

what is up there? If we could do it, because if it is not, I am going to erase it and here we go again.

DR. FEDORKA-CRAY: The only way that I would qualify it for the future and say -- if technology becomes available, you know, to select. What you are talking about is a sentinel organism, you know. But the limitations would be that it would be drug dependent, strain dependent, serotype dependent, phase type dependent. It may not adequately reflect field conditions.

CHAIRMAN WAGES: You know, if it is an if and an if and if, if the dog stopped, he would have caught the rabbit.

DR. FEDORKA-CRAY: That is just it. We are not there yet. I think that one of the things would be to look and say where can you -- if you have to get the process moving now, what can you do right now to get the process moving to insure that there is no risk?

CHAIRMAN WAGES: And that is not a way to go.

DR. FEDORKA-CRAY: We are not there yet.

CHAIRMAN WAGES: Is that a consensus?

(Chorus of "I agree.")

CHAIRMAN WAGES: Okay. Then hit the space key. Okay. So, back to the question. You have got the decision-making potential in your hand and you want this information. Are there ways that are in existence or not in existence, potential, practical, possible, that you would

recommend, whether it be pre or post-approval? Richard.

DR. CARNIVALE: I don't know if this is exactly on point, but I wanted --

CHAIRMAN WAGES: I really doesn't matter.

DR. CARNIVALE: I shouldn't say that. I think it is pretty closely related. I wanted to pick up on something Jeff said and I have heard some other people in the past from CVM say.

The concern they seem to have is that we recognize resistance development -- susceptibility changes I should say is frequently a long-term event with most drugs and most compounds. There are exceptions to that. We could never really run a study to really predict what may happen to a drug two years, five years, 10 years down the road. That is what post-approval monitoring is really to do.

However, the concern that reviewers have is whether they are going to put something out that is going to create rapid and massive resistance right away to particularly important food-borne pathogens, be it camplyobacter, E. coli or salmonella or what other emerging pathogen comes down the road.

So it seems to me maybe that is where we ought to focus. Is there a way we can get data to give the reviewers some assurance that this drug is not going to cause that kind of very rapid, very massive resistance at the label dose?

Can that be done in an in vitro setting? Well, we already have that information from items one and two.

Or is there another kind of study that can be run to give that reviewer some assurance that he is not putting a time bomb out there, recognizing that he is never going to be able to predict how susceptibility is going to change over the years. But at least he can have some assurance that it is not going to cause really rapid resistance in particular pathogens right away.

CHAIRMAN WAGES: Okay. Are there in vitro tests out there that have some -- it is still a predictive value at least. You are talking about a predictive value of fast versus slow, dynamite versus firecracker.

DR. CARNIVALE: It is acute versus chronic, if you will. I mean, is there some kind of acute effect that you can measure?

DR. McDERMOTT: See, these are mechanism dependent as well though. (Away from mike.)

CHAIRMAN WAGES: Are fluoroquinolones fast to --

DR. McDERMOTT: No.

CHAIRMAN WAGES: Why do you say that?

DR. McDERMOTT: Well, in vitro they mutate infrequently to high levels of resistance.

CHAIRMAN WAGES: Okay. And that is in vitro. See, that is what I am saying. Okay. Would you take that to you?

Would you take that information --

DR. MEVIUS: Not in vitro in camplyobacter. That is very rapid.

CHAIRMAN WAGES: But see, you know that. What I am saying is we do know that, and now we know that in vitro it is made predictive with one organism and it is organism specific. Is there enough information out there? Sure. No, you can't do it with campy, but you could do it with whatever.

Could you feel comfortable taking study information and are the capabilities there, or could they be there, to take that to CVM where they are comfortable with it? You know, this is just not going to show up fast because this class of compounds, historically, has not been rapid. Maybe you can't, but --

DR. McDERMOTT: I would be reluctant to say you could based on ---

CHAIRMAN WAGES: So you wouldn't feel comfortable taking a package in and saying, this is fluoroquinolones, pretty slow, all of it has been slow, in vitro says it is slow, this is no different. You would not feel comfortable taking that, as a sponsor, in it?

DR. McDERMOTT: I think we are limited here by the unknowns, which -- one other thing that I think is valid about the animal studies is to get a handle on not just the

rate necessarily, because we don't know how predictive that is, but just the catalog of mechanisms available, because it matters whether you have plasmid borne resistance versus chromosomal.

CHAIRMAN WAGES: I asked you a question about fluoroquinolones or whatever, and you said, oh, yeah, it happens. And you have got some study that tells you you would be comfortable going to them and saying I have got drug and it shouldn't blow up in our face and post-approval monitoring should be sufficient to predict or to show us something happened.

DR. McDERMOTT: I would like to see it in vivo. Personally, I would like to see those numbers derive somehow in vivo if possible.

CHAIRMAN WAGES: Okay. So, we would like to see the potential for in vitro and in vivo studies to help -- help me out here. I don't want to put words in your mouth.

DR. KOTARSKI: Can I just offer a brainstorm idea? I have a real quick idea and see how this flies. Okay. I do a literature survey. I have got indications from my literature survey that the chances for resistance emergence are pretty low. I do pilot studies, and I kind of confirm that with my effective dose. Very small studies. Okay?

And I go, I did some small studies, everything seems to fit together. What I would like to do then is give

my efficacious dose with a group of animals and then follow them to slaughter and say -- you know, and just assay what is at the slaughter. What is isolated from the carcass. Not during transfer or just before you put it in. Isolate it from the carcass. Do I see resistance here?

Just confirm that within one course of therapy for a group of animals -- that I don't see resistance on the carcass. That is a brainstorm.

DR. KRUSHINSKIE: I think that is really short and sweet and to the point. I think really -- especially if we are not eliciting anymore ideas on what we can do in vivo. Ninety-nine percent of what you need to know you are already going to have after one and two.

You already know your mechanism, you already know -- you know related organisms. You know everything about it. And now, what you are really looking for is something to just basically confirm it, because there is no way to predict absolutely what the outcome is going to be. And there aren't any obvious molecular studies that we just haven't dreamed up. You know, nobody has volunteered; no great person in the room.

CHAIRMAN WAGES: So you are comfortable.

DR. KOTARSKI: I am brainstorming.

CHAIRMAN WAGES: Yes. But you could be -- I am already dead. So -- go ahead.

DR. MEVIUS: I think that is a very good idea. But then you come up with a point; that if you find resistance, what then? Then you are at the end of your development. You have invested an enormous amount of money. Then you still want to know is this the optimum dose? Are there other doses or regiments left that would not select resistance --

CHAIRMAN WAGES: But see, I think that -- if I am Wages Pharmaceutical developing a compound, knowing the environment, the first dag blasted thing I am doing is figuring out what the resistance are. Put it in -- some basic things to look at that.

If I came to the pre-approval stages just trying to identify that -- see, I don't think the -- some of our arguments is not germane to that compound has already been looked at, and we have got a pretty good chance that this thing is going to go through, except with some questions. So some of that is real -- that is really pre pre-approval.

DR. KOTARSKI: And the key would be --- pilot studies to --

CHAIRMAN WAGES: I am just -- my question was there ways that you could be comfortable as a sponsor or as a researcher or even, I guess, from CVM. And I know you guys want to -- what would be a comfort zone? Would you feel, as a scientist, going in and saying, hey, this is what we have done. We have done some trials that looks like, at least in

a treatment standpoint, it is found on the carcass. Looks good, it supports our in vitro work, bingo. We have a stringent post-approval monitoring and that is what keeps coming through, to look at potential changes and for mitigation strategies that occurs. Bingo.

DR. KRUSHINSKIE: It seems to me that the paradigm shift here from the current system to the proposed system is to include antibiotic resistance as one of the safety items. Is it not true that fluoroquinolones -- and I don't know all that much about them. Maybe I am wrong.

Do we look at camplyobacter in the pre-approval process?

CHAIRMAN WAGES: No.

DR. KRUSHINSKIE: See. So now we are saying, okay, let's include that in our package. Doesn't that solve the problem? We are confident that is going to be one of the criteria? Because that was the problem before. Nobody looked. It wasn't part of the process.

DR. FEDORKA-CRAY: I think that you are going to have to have -- you know, in doing those types of things, you are going to have to split the species and -- but I think that what you are doing is changing the paradigm of how companies probably develop drugs now in the first place, and you are going to have a much better idea about species, specificity and what not.

So, if you would bring -- you know, just from a research standpoint, if you would bring to the table that you have done this test in these types of conditions and this is your -- this is your generated rate of resistance, I think that would be an adequate check, because you can't put in enough of -- you can't test it enough to know what is going to happen when you put it out into the field to know how all the other variables are going to effect everything.

So I think that doing that type of study where the company is probably looking at all of these issues now, because they can't afford not, and that they --

DR. KRUSHINSKIE: They can't afford to wait until the end.

DR. FEDORKA-CRAY: Right. They can't afford to wait until the end. So then they come and they do this study with a larger -- say a 500 flock, a 500-bird flock or something. You know, not a 10 or 20, but something that would give some statistical power to it or something and then say this is the rate of -- or this isn't the rate we are getting. Then that would be -- at least from a scientific standpoint, that would hold up.

Now, the question I would have along those lines though would be just say that you had a percent of -- I mean, we know that any time you use a drug there is going to be resistance that occurs in some bacteria. Okay?

So, if you have your little list and it just so happens that there is resistance that occurs in one of those species, what will the comfort level be for seeing that resistance, as far as, you know, saying there will still be some merit in having the drug come to market?

In other words, say you had a three-percent resistance in camplyobacter with the fluoroquinolones when they came. Is that going to -- how will the process be generated then to say that that is still acceptable?

DR. KRUSHINSKIE: That is where the dose optimization should be looked into.

DR. FEDORKA-CRAY: Right. But that is all done. But what I am saying is if, in fact, a drug is developed with the likelihood that there is going to be resistance in some bacteria -- if you have got your panel and you are looking at it, in bringing some resistance to the table, how comfortable -- you know, what are you looking -- what is -- what are you looking for? What is FDA is looking for when it comes to saying this is okay to put it out to the field?

And I think that still has to be approached and some dialogue to go on about that, because you have absolutely no idea, I mean, when you start talking about all this resistance stuff and everything. And if you get in -- you don't get it in campy, you don't get it in salmonella, you get it in E. coli, you don't get it in enterococci, and

somebody says, well, now you have a bacteria that has some tendency for transfer to occur, well, we really don't know what the rate of transfer might be because those are studies that would take long periods of time to have that answered under, you know, some conditions. Is that still going to be enough?

CHAIRMAN WAGES: We may not answer that.

DR. FEDORKA-CRAY: I know. But that is a question that still has to be --

CHAIRMAN WAGES: It is 10 to 12:00. We are going to have to cut bait here.

MS. : I think that was the point that Bill made in his presentation about the fact that we need to obviously develop what we call interpretive criteria, which is exactly -- gets to your point. How? What are we going to compare that to? What is going to be acceptable and what is not?

I actually had a question for you, Sue, in terms of your comment on the studies. Were you envisioning that was like a one-time treatment or a multiple treatment when you were --

DR. KOTARSKI: When I was brainstorming?

MS. : Yes. Just a second ago. Because, you know, you just -- if you treat once, which is maybe less indicative, you know, you may not be looking at the

environmental contamination and recontamination of other animals. So I just wondered, in terms of brainstorming, more detail on that.

DR. KOTARSKI: Okay. If I got to a point where I said all indications are I have got a pretty good effective dose, and I know I have got a little resistance emergence here that happens during the time that I treat -- like maybe I am working with a one-day-old bird and I see a resistance emergence, well, it could be that that resistance occurs but it fades out because there is different populations that come in or whatever.

So I don't know how to interpret what that means or I didn't see anything, and I am not sure overall because there is another information that says reverse resistance emergence occurs.

If I go for my final field trials or whatever, I say, okay, I am going to do a multi-study, I am going to treat the animals at the ages indicated with my effective dose, all the indications I have so far as I have gone through this process is in pilot studies. Not in --- studies, but small studies. They should be okay.

The confirming would be I give the dose in the multi-field and then those animals get followed up at slaughter when you find out what is on the carcass, just to give some -- because the question is up there that came up

several times. What does this mean for human safety?

DR. CARNIVALE: Just a question. Are those animals you are following to slaughter -- you know they are infected with food-borne pathogens?

DR. KOTARSKI: No. This is field conditions of treatment. The age -- you know, field use conditions.

DR. CARNIVALE: Well, what if you don't find anything?

DR. KOTARSKI: Absolutely. That is the point.

DR. CARNIVALE: No. What if you don't recover any pathogens?

DR. KOTARSKI: That is the point, is that I have some information for my risk assessment; that the likelihood that when I use this treatment for -- now I am brainstorming again. That, you know, for treatment I am or I am not impacting health --

DR. CARNIVALE: But that is just in a small group of birds. That doesn't tell you --

DR. KOTARSKI: No. I said multi-field.

CHAIRMAN WAGES: Okay. Right now, time out. We are talking about the last 60 seconds. It is fourth and goal, and we are in trouble.

Is there anything that -- from an alternative standpoint that you all want listed up there that you want me to say this afternoon? Not brainstorming or -- you could be

brainstorming, but is there anything that you want to go and print? Then we will go back to the -- you know, having a good time.

DR. LUTHER: I like Sue's brainstorm idea. Did we capture that?

CO-CHAIRMAN GRAU: That is the question.

CHAIRMAN WAGES: If you want it captured, we will put it on there.

DR. WEBER: Did she mean at slaughter -- you said carcass. I thought we were also interested in fecal material, because there is a potential to contaminate. Not being a chicken guy, I don't know what the relative success would be or -- comparative between those two.

CHAIRMAN WAGES: Where do you think the bacteria comes from that is on the carcass?

DR. WEBER: No. But do they not put some out into the litter that goes into the next group that comes here? I mean, as far as the ability to detect it, how does that work?

DR. FEDORKA-CRAY: I think that what you are going to get yourself caught up into is how many times -- this is where the whole --

CHAIRMAN WAGES: Okay. Time out. Who cares? Does it matter?

DR. FEDORKA-CRAY: Well, it matters if it is -- it matters if someone is asking the question if there is an

environmental aspect that is associated with it, and that comes down to the point of -- I think that is where the post-approval monitoring process becomes absolutely crucial.

The question I would ask you, Nick, is how many times do you have to do that to get the desired effect? And we may not know under all the conditions. Concurrent disease and environmental and management and all of that. So you are giving your best guess as to whether there is any effect to the drug.

DR. WEBER: My only question -- and I am not even sure I am aware of the total protocols that have been discussed. But I am assuming that the -- a number of bacteria. To look for resistance per gram of fecal material as opposed to per gram of rinsed surface carcass.

DR. KRUSHINSKIE: You don't market fecal material. We have never accepted the premise that antibiotic use in food producing animals leads to resistance among the food-borne pathogens in humans. We have never verified or validated that premise to begin with.

MS. : And the comments haven't been addressed for the risk assessment model, and we are in here now developing a pre-approval process that some of us addressed in our comments that aren't in agreement with.

DR. WEBER: Well, part of the issues was getting information on the resistance determinants that this might

have, with the idea that you may be able to look at and follow them into potential development of a resistance in humans.

I believe, at least in some European experiences, they have been able to track the coincidence of determinants in both animals and humans.

DR. KRUSHINSKIE: There is a kill step between the production of raw carcasses and the consumption of poultry meat, and some of that is never taken into consideration. So I think this whole argument is esoteric.

DR. WEBER: We have got to collect some data so we can bring some real data to bear on it. That is what people like CDC and other interested parties are saying. And if you don't have some of those things, we just can't say, well, we don't know. They say, well, then do something until you do know.

CHAIRMAN WAGES: Okay. Susan, go ahead. Do you want to capture what --

DR. KOTARSKI: What do you want me to do?

CHAIRMAN WAGES: Do you want to put your brainstorm up there? Is that kind of what it --

DR. KOTARSKI: Okay. If indications are -- the flock treated was -- field trials under use conditions; effective dose yield carcasses with resistance organisms.

DR. WEBER: And again, I register a concern about

that.

CHAIRMAN WAGES: I don't know if I would feel comfortable standing up and defending that one way or the other. I don't know what it is.

DR. KRUSHINSKIE: --- animal studies --- we have got a lot of questions on how we would even do those.

CHAIRMAN WAGES: Treat it with drug per use conditions, test for treatment, --

DR. MEVIUS: Not testing for the treatment.

DR. KOTARSKI: Test the zoonotic -- test bacteria on the carcass for resistance.

DR. GILBERT: Just end point, no product. Right?

DR. KOTARSKI: Right.

CHAIRMAN WAGES: Is that what people want to be explained this afternoon? How many people want that to be explained this afternoon? Raise your hand.

(Show of hands.)

CHAIRMAN WAGES: Three. How many don't?

(Show of hands.)

CHAIRMAN WAGES: Two. Okay. Well, what is the other bunch?

(Laughter.)

CHAIRMAN WAGES: If it is three to two, it is not going to go up there, folks, because that means that it is not a big deal for this group as a whole.

CO-CHAIRMAN GRAU: Are you saying the group isn't ready yet to put forward any sort of --

DR. KRUSHINSKIE: Right.

CHAIRMAN WAGES: Then scratch if. Take it off.

(Simultaneous conversation.)

MS. : You are not supposed to have to reach consensus on what the points are.

CHAIRMAN WAGES: Well, if I can only get three or two people to vote on it, it is not going up there. Period. End of report.

DR. KOTARSKI: I have another brainstorm. This one has less implications for registration. I know that is why people are reluctant to even bring it up here.

Does anybody want to incorporate in that early information package literature review, and I emphasize the word literature review, in human medicine for risk factors for resistance to dispersion or whatever?

I mean, if we are going to -- category one, that means it is a unique drug. And usually in human medicine, when you have a quintessential drug, that start identifying risk factors for use for resistance emergence. And a lot of times that literature is out there and sometimes they get you some clues about use practice that might be applicable to humans or animals, and it may not be.

CHAIRMAN WAGES: Okay.

MR. : Nicely pointed out.

MR. : Dennis, do you have enough to --

CHAIRMAN WAGES: I am totally confused.

(Simultaneous conversation.)

CHAIRMAN WAGES: We will do the best we can. I would encourage, in the public comment, if things aren't addressed to the satisfaction of some of you -- and I think -- in all due respect, I think we have got most of the information that this group wanted up there. I wasn't near as bad as I sounded, Dr. Thompson.

It is getting late. But, if I don't, please do that at that time in the public comments, because I will tell you right now, folks, if I was an expert in what we talked about and we were talking about excessive feed conversion changes in a broiler, I could do it.

But we are talking about things that are a little bit out of my expertise, and I am going to rely on the information that we were given and do the best I can in presenting your views. But, please. And I would also say, if you can change the moderator who is going to present, I would do so now.

You know, I will do the best I can, and I will do it over the lunch hour and present it to the best of my ability. But, please, feel free to comment in the open period, especially if I didn't justify or prioritize

something good enough. That is what I am more afraid about. And, thank you very much for everything.

(Whereupon, at 12:00 p.m., the breakout meeting was concluded.)